THE NUTRITIONAL RISKS OF CHILDREN WITH CANCER

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Abbreviations

AgRP	Agouti Related Peptide
ALL	Acute Lymphoblastic Leukaemia
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute Myeloid Leukaemia
ANOVA	Analysis of variance
APR	Acute Phase- Response
AR	Adiposity rebound
ATP	Adenosine triphospate
BIA	Bioelectrical impedance analysis
BMI	Body Mass Index
BMR	Basal metabolic rate
BW	Body weight
CI	Confidence of Interval
CML	Chronic Myeloid Leukaemia
CNS	Central Nervous System
CRP	C reactive proteins
CRT	Cranial Radiation Therapy
Cu	Copper
CVD	Cardio Vascular Disease
d	day
DEXA	Dual-energy X-ray absorptiometry
DRV	Dietary Reference Value
EAR	Estimate Average Requirements
EFS	Event Free Survival
EN	Enteral nutrition
ESPEN	European Society of Enteral and Parenteral Nutrition

ESPGHAN	European Society for Paediatric Gastroenterology and Nutrition
FFM	Fat Free Mass
FM	Fat Mass
GCT	Germ Cell tumour
GGT	G-glutamyl transferase
GHD	Growth Hormone Deficiency
GI	Gastro Intestinal
Gy	Gray unit
H	Height
hsCRP	High sensitive c-reactive protein
H/W	height for weight
H/A	Height for age
HR	High risk
ICC	Interclass Correlation Coefficient
ICCC-3	International Classification of Cancer
ICW	Intra cellular water
IGF-1	insulin like growth factor-1
IGFBP-3	IGF binding protein 3
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-8	Interleukin-8
IQR	Inter quartile range
JT	Jejunal tube
Kcal	Kilo calories
Kg	Kilo gram
Kj	Kilo joule
LBM	Lean body mass
LEPR	Leptin Receptor

LMF	Lipid Mobilising Factor
LR	Low risk
MF-BIA	Multi frequency BIA
MUAC	Middle upper arm circumference
MUST	Malnutrition Universal Screening Tool
NDNS	National nutrition and diet survey
NPY	Neuropetide Y
NS	Nutrition support
NST	Nutrition support team
OR	Odd ratio
OS	Oral supplements
PA	Physical activity
PA	Pre albumin
PAL	Physical activity level
PEG	percutaneous endoscopic gastrostomy
PIF	Proteolysis-inducing Factor
POMC	pro-opiomelanincortin
PTH	Parathyroid hormone
PYMS	Paediatric Yorkhill Malnutrition Score
QMU	Queen Margaret University
QoL	Quality of life
RBP	Retinol binding protein
RDA	Recommended Daily Allowance
REE	Resting Energy Expenditure
RHSC	Royal Hospital of Sick Children
SDS	Standard Deviation Score
SF-BIA	Single frequency BIA
SGA	Subjective Global Nutritional Assessment

SGA	Subjective Global Assessments
SS	Symptom Score
STAMP	Screening Tool for Assessment of Malnutrition in Paediatrics
TBW	Total body water
TEE	Total Energy Expenditure
TEM	Technical error of measurement
TNFα	Tumour necrosis factor
TPN	Total parental nutrition
TRM	Treatment Related mortality
TSF	Triceps Skin Fold
UAFA	Upper arm fat area
UAMA	Upper arm muscle area
UK	United Kingdom
W	Weight
W/A	weight for age
W/H	Weight for Height
WBPT	whole blood protein turnover
Zn	Zinc

Declaration

I declare that the work contained within this thesis is original. I have solely been responsible for the organisation of the study herein, as well as all aspects of data collection and the analysis of results, unless otherwise stated.

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Abstract

Nutrition is a major concern in paediatric cancer, increasing the risk of co-morbidities, affecting tolerance of therapies and influencing survival. Despite this, very few studies have aimed to identify the nutritional risks of children treated for cancer in the western world.

A unique retrospective study was therefore proposed to assess the degree of nutritional risk in paediatric cancer using the need for nutrition support (NS) as a proxy for high nutritional risk. Of 168 patients, seventy four (44%) required NS of whom 50 (67%) and 24 (33%) had solid and haematological malignancies. These findings underline the common need for NS in this childhood cancer cohort.

A prospective study was consequently designed to assess the effect of cancer and its treatment on nutritional status, using commonly used assessment techniques. Measurements were taken regularly at six time points over a period of up to 18 months. 26 patients, 18 (69%) male and 8 (31%) female (median age 5.1; IQR 2.3, 7.9) volunteered for the study. At recruitment and during the first three months of treatment, those with solid tumour demonstrated nutritional deprivation, low BMI (median 25.5, IQR 5.5-60.5; median 18.0, IQR 7.5-54.2 respectively), low fat mass %(median 76.3, IQR 48.5-99.1; median 70.8, IQR 62.6-124.8 respectively), low energy intake (median kcal/d 1200, IQR 866-1970; median 1305 kcal/d, IQR 901-1488) and a high need for NS. In contrast, those with haematological cancer demonstrated an excess BMI (median 66.0, IQR 41.5-82.2; median 79.5; IQR 70-94.2 respectively), high fat mass % (median 102.0, IQR 78.6- 153.0; median 129.4, IQR 96.5-202.6,respectively) and excessive energy intake (median kcal/d 2076; IQR 1453-2525, median kcal/d 1078, IQR 919-1206 respectively)

These results suggest that children undergoing cancer therapy are at high risk of both undernutrition and obesity and they indicate apparent differences in nutritional risk according to diagnosis and treatment.

Key words: Children, cancer, nutritional status, nutrition screening, malnutrition

1 CHAPTER ONE

REVIEW OF THE LITERATURE

1.1 INTRODUCTION

During the critical period of growth and development in the life of a child, optimal nutrition is essential. A diagnosis of cancer during childhood modifies the body's nutritional needs and therefore it can affect the ability of the child to achieve optimal growth and development. Cancer treatments can also independently affect a child's nutritional status at certain stages of the disease (Murphy et al. 2009). Whilst children are treated for cancer, these factors can be very significant as their growth and development must be sustained. Furthermore, undernutrition during cancer can increase morbidity and mortality (Mejia-Arangure et al. 1999; Reilly et al. 1994) which, in turn, causes decreased quality of life (QoL) and increased health care costs (Agostoni et al. 2005). It is becoming increasingly apparent that appropriate nutritional care (comprising nutritional assessment and nutrition support) is vital to ensure optimal growth from the stage of birth to the end of puberty during cancer therapy (Agostoni et al. 2005). Despite these facts, the evidence base on nutritional care in children and young people with cancer is scarce and fragmented.

The prevalence of undernutrition has been described at different stages and in specific diagnoses (Garofolo et al. 2005; Mejia-Arangure et al. 1997; Reilly et al. 1999; Yaris et al. 2002). However, a limited amount of evidence exists to determine the overall risk factors for the development of undernutrition such as age at diagnosis, gender, type of tumour, stage of tumour, treatment modalities and protocols in children treated for cancer. Therefore defining the risk factors for undernutrition in cancer patients is now pivotal.

Overnutrition also has detrimental effects during cancer therapy. It has been suggested that obesity during cancer therapy can increase the risk of mortality,

morbidity and chemotherapy induced toxicity (Butturini et al. 2007; Lange et al. 2005). Additionally, survivors of childhood Acute Lymphoblastic Leukaemia (ALL) seem to gain weight excessively during and after therapy and become overweight and obese (Ventham and Reilly 1999). With the increased number of people who survive childhood cancer, long term nutritional consequences are becoming a new concern for this particular cohort. Hence, the maintenance of growth and development, the monitoring of nutritional status, as well as the prevention of chronic issues such as obesity, are now essential goals for oncology practice. This introduction will provide an overview of childhood cancer and its treatments and it will focus on the nutritional issues, nutritional risks and nutritional management of children treated for cancer.

1.2 Childhood Cancer

Cancer or neoplasm is a life threatening illness characterised by an unregulated cell growth (Kumar et al. 2006). A neoplasm can be classified as benign or malignant according to their ability to metastasise to other organs. Malignant tumours grow uncontrollably and spread to other parts of the body whereas benign tumours do not (Kumar et al. 2006).

Cancer is the most common cause of disease related deaths in children in the western world (Cancer Research UK 2012) with the majority of childhood cancers being malignant (93%). The non-malignant brain tumours are included in the classification of childhood cancer because they are generally treated the same as malignancies and they can also be life threatening (Information Service Division Scotland 2012). Figures from the 2006-2008 period show that around 1550 children in the UK were diagnosed each year and of those around 260 children died each year including non-malignant brain tumour (Cancer Research UK 2012). Considerable improvement in treatments during the past few decades has dramatically increased the survival rate at five years from around 28% in the sixties to around 80% currently. At the end of year 2000 in the UK there were more than 26000 people who had in the past been diagnosed with some type of childhood cancer. The survival rate at ten years does not differ from those at five years with the leading cause of death among childhood cancer survivors being the recurrence of the original cancer followed by cardiac and

pulmonary treatment related complications (Mertens 2007). Hence, with the increased number of people who survive childhood cancer, the long term consequences of the disease and its treatments need to be prevented whenever possible.

For treatment and research purposes childhood cancer is classified according to the International Classification of Childhood Cancer (ICCC-3) (Steliarova-Foucher et al. 2005). This classification is based on morphology and consists of 12 main diagnostic groups. Each of the broad 12 diagnostic groups has numerous subgroups. The Leukaemia group includes all the haematological malignancies which are defined as those cancers affecting the haematopoietic tissue causing an abnormal increase of immature blood cells (Brooker 1994). Leukaemia is the most common diagnosis of childhood cancer (Cancer Research UK 2012) and it can be classified in three sub-types: Acute Lymphoblastic Leukaemia (ALL), Acute Myeloid Leukaemia (AML) and Chronic Myeloid Leukaemia (CML) (Steliarova-Foucher et al. 2005). ALL includes patients with high risk disease (high risk ALL) and low risk disease (low risk ALL). Survival rates are much lower for patients with high risk disease compared to the low risk.

The most common childhood solid tumours are those of the brain and central nervous system (CNS) (both malignant and non-malignant), which account for 22% of all childhood cancers overall, followed by Lymphoma, accounting for around 19% of the total cancers (Boon et al. 2006; Cancer Research UK 2012; Information Service Division Scotland 2012). Even though benign tumours do not metastasize, they are life threatening because they grow on a limited space causing obstruction and pressure on the brain which leads to increased intracranial pressure, seizure and eventually death (Boon et al. 2006). Figure 1.1 shows the incidence and mortality rate expressed as percentage of total childhood cancers in the UK (Cancer Research UK 2012). The incidence and mortality data for the Scottish population reflects the national data (Information Service Division Scotland 2012).

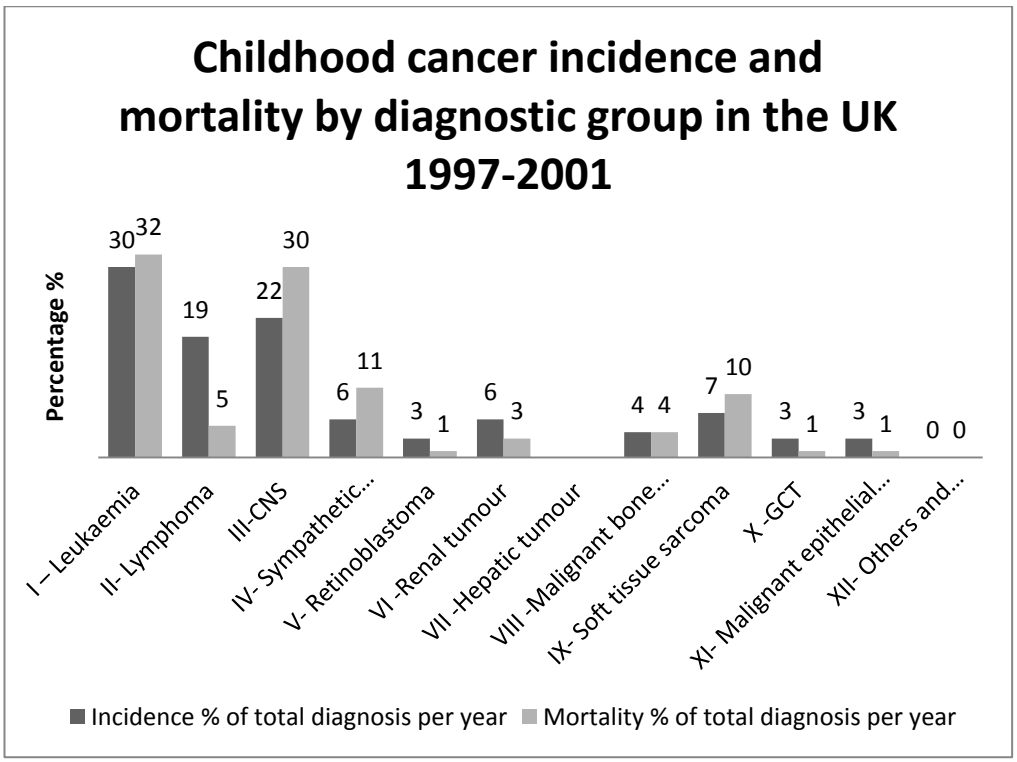


Figure 1.1 Incidence and mortality percentage rate in the UK according to diagnosis using the ICCC-3 classification (Cancer Research group 2004).

The management of childhood cancer is very complex and it aims to achieve a cure whilst minimising pain and adverse effects of treatments. The main treatments for cancer are chemotherapy, radiotherapy and surgery; they can be used singly or in any combination. Chemotherapy targets dividing cells, both healthy and cancerous (Pui and Jeha 2007). Radiotherapy consists of the use of radiation to destroy multiplying cells and surgery removes the cancer from the body (Chan 2007). Children with cancer are generally treated in clinical trials or standard regimens and the treatments are often combined. However, the most recent practice is to avoid radiotherapy whenever possible in this cohort as children are more prone to long term effects which include learning disabilities, stunting bone growth, and lung and heart damage depending on the irradiated area; therefore it should be used in children only when there no other options are available (Oeffinger and Hudson 2004). In particular, cranial irradiation therapy (CRT) was used in the past to prevent central nervous system (CNS) relapse in ALL. However, in the more recent treatments prophylactic CRT has been omitted (Chan 2007) to avoid the detrimental effect.

Specificity of treatments in children is necessary because childhood cancers differ from adult cancers in many aspects including type, pathology, treatments and survival rate. Adults cancers are mainly carcinomas of different tissues, whereas most of the common childhood cancers are embryonal in origin, their cells are undifferentiated and still capable of differentiating in different type of mature tissue, which makes them more responsive to treatments. Furthermore, children tend to have acute forms of lymphomas and leukaemia compared to adults who tend to have the chronic form (Chan 2007). All of these aspects, in addition to the fact that children are developing and growing individuals, hopefully with many years of life ahead, make this patient group unique and very complex. This is especially relevant when considering this disease in relation to nutritional risk. However most of the research published in this area, especially in cancer cachexia and energy metabolism and has been carried out in adults (Falconer et al. 1994; Hyltander et al. 1991b; Moses et al. 2004; Nixon et al. 1988). This is largely due to the methodological limitations of measuring children and to the smaller incidence of cancer in children compared to adults. Because of this lack of evidence, in writing this document it has often been necessary to refer to the adult literature available. However, it is not always clear whether such findings can be directly applied to the paediatric cohort and therefore the interpretation of the results must be done with caution. Furthermore the paucity of paediatric research underlines the necessity for studies designed to explore the nutritional risks related to cancer in this specific cohort.

1.3 Malnutrition in children with cancer

Malnutrition occurs when there is a deficiency (undernutrition) or excess (overnutrition) of energy, protein and other macronutrients and micronutrients which causes adverse effects on the body's functions and results on a poorer outcome (Joosten and Hulst 2013). However the term malnutrition is often wrongly used as synonymous to that of undernutrition. In this thesis, the term malnutrition will only be used when it refers to both undernutrition and overnutrition.

The extent to which nutrients are available to meet metabolic needs is referred to as nutritional status. Nutritional status is determined by the availability of nutrients in the body and their utilisation to maintain health and growth (Shaw and Lawson

2007). Body weight homeostasis is regulated by the energy balance equation. Total energy expenditure (TEE) is composed of resting energy expenditure (REE) accounting for 60-70% of energy output, physical activity (PA) (15-30%) and diet induced thermogenesis (7%-13%). The fat free mass (FFM) or lean tissue is the metabolic active component of the body and intrinsically relates to REE (Elia 1992a). When energy balance is disrupted and energy intake does not meet the energy expenditure over a long period of time, the body energy stores are utilised to meet the energy requirement leading to weight loss. This negative energy balance weight can lead to undernutrition. However, when energy intake exceeds the energy expenditure over a long period of time the body is in positive energy balance and the excess energy is converted into fat stores, causing increased body weight which can eventually lead to obesity (Macdonald 2007). Childhood malignant disease and its treatments can dramatically disrupt energy balance causing both undernutrition (Carter et al. 1983a; Donaldson et al. 1981; Garofolo et al. 2005) and obesity (Reilly et al. 1998; Reilly 2009; Ventham and Reilly 1999) with detrimental consequences to growth, development, morbidity and mortality (Donaldson 1982; Lange et al. 2005).

1.4 Undernutrition in childhood cancer

Energy requirements vary throughout life stages. From conception to adulthood, cells turnover very fast and many essential nutrients and energy are required to support cell division, growth and development. Therefore, during this period energy balance should be positive and energy intake must meet the energy requirement to support this anabolic state. Children's growth is characterised by alternating phases in which the body accumulates nutrient stores followed by a phase of growth. As a result, if the demand for nutrients to support continuous growth cannot be met solely by the nutrient intake there is a reliance on the nutrient stores previously accumulated (Whitney et al. 1987). An inadequate supply of nutrition at any time during childhood cancer can therefore impact on optimal growth and development.

Undernutrition can be classified as acute and chronic, depending on the length of the energy deprivation. In children, when nutritional deprivation begins, the first measurable body change is a decrease in body weight (acute undernutrition)

whereas, when the nutritional deprivation persists and the energy intake is insufficient to sustain growth and development, growth impairment will occur resulting in a deficit in length and height (chronic undernutrition) (Waterlow 1972). Furthermore, a poor or absent weight gain and the failure to maintain a growth trajectory can also indicate acute undernutrition. This inadequate growth in childhood is defined as failure to thrive (Waterlow 1972). In children treated for cancer, the disease and the therapy can cause both acute and chronic undernutrition (Brennan 1998). It is therefore pivotal that during childhood cancer treatments, acute undernutrition is promptly detected and nutritional intervention quickly initiated to avoid chronic undernutrition with consequent growth and development impairment.

The pathophysiology and consequences of undernutrition in disease are more complex and multifactorial than in health. Undernutrition in disease can be associated with disease severity and can be a consequence not just of decreased intake but also of altered nutritional requirement, decreased absorption, inflammation and difficulties in feeding (Macdonald 2007). A further distinction is essential when the disease in question is cancer. Contrary to other diseases, where there is the involvement of a single organ or system, (e.g. kidney, GI tract) cancer and its treatment can affect nearly every organ thereby having more widespread significant nutritional consequences (Bozzetti et al. 2000). In addition, the scenario becomes even more complex when we consider that, compared with adults; children treated for cancer have additional needs to support continuous growth and development.

Undernutrition is common among hospitalised children, however it is often unrecognised and therefore not treated (Agostoni et al. 2005). Many paediatric oncology patients become undernourished at some stage of the disease (Murphy et al. 2009) and the manifestation of undernutrition in paediatric cancer is often insidious and may be not identified. This is because the presence of oedema fluid retention and the weight of the tumour itself may mask undernutrition especially when assessed by weight related techniques (Pietsch and Ford 2000; Smith et al. 1991).

The exact prevalence of undernutrition in childhood cancer patients is unknown. Prevalence figures vary considerably from around 10% to 50% (Carter et al. 1983a; Carter et al. 1983b; Pietsch and Ford 2000; Smith et al. 1991; Uderzo et al. 1996). The heterogeneity of diagnosis, different stage of treatment, treatment protocol, definition of undernutrition used, and methodology used to assess nutritional status make an accurate estimate very difficult. Moreover the rate of undernutrition for the general population varies dramatically between countries and, with many studies carried out in developing countries, the undernutrition rate reported in some studies must be interpreted in relation to the regional prevalence of undernutrition, making the quantification of prevalence of undernutrition even more difficult. The assessment of prevalence of undernutrition is important to identify and target causative factors. The difficulty of estimating the prevalence of undernutrition is a major limiting factor in research in this area.

Cancer associated undernutrition is a complex and multi-factorial phenomena. Factors implicated in the development of undernutrition in childhood cancer are: reduced dietary intake, malabsorption and altered metabolism (Figure 1.2). These factors can results from the host response to the cancer itself, the anti cancer therapy or the effects of the cancer itself on metabolism (Balducci and Hardy 1985). These detrimental factors can act as single cause or combined leading to a greater risk of undernutrition.

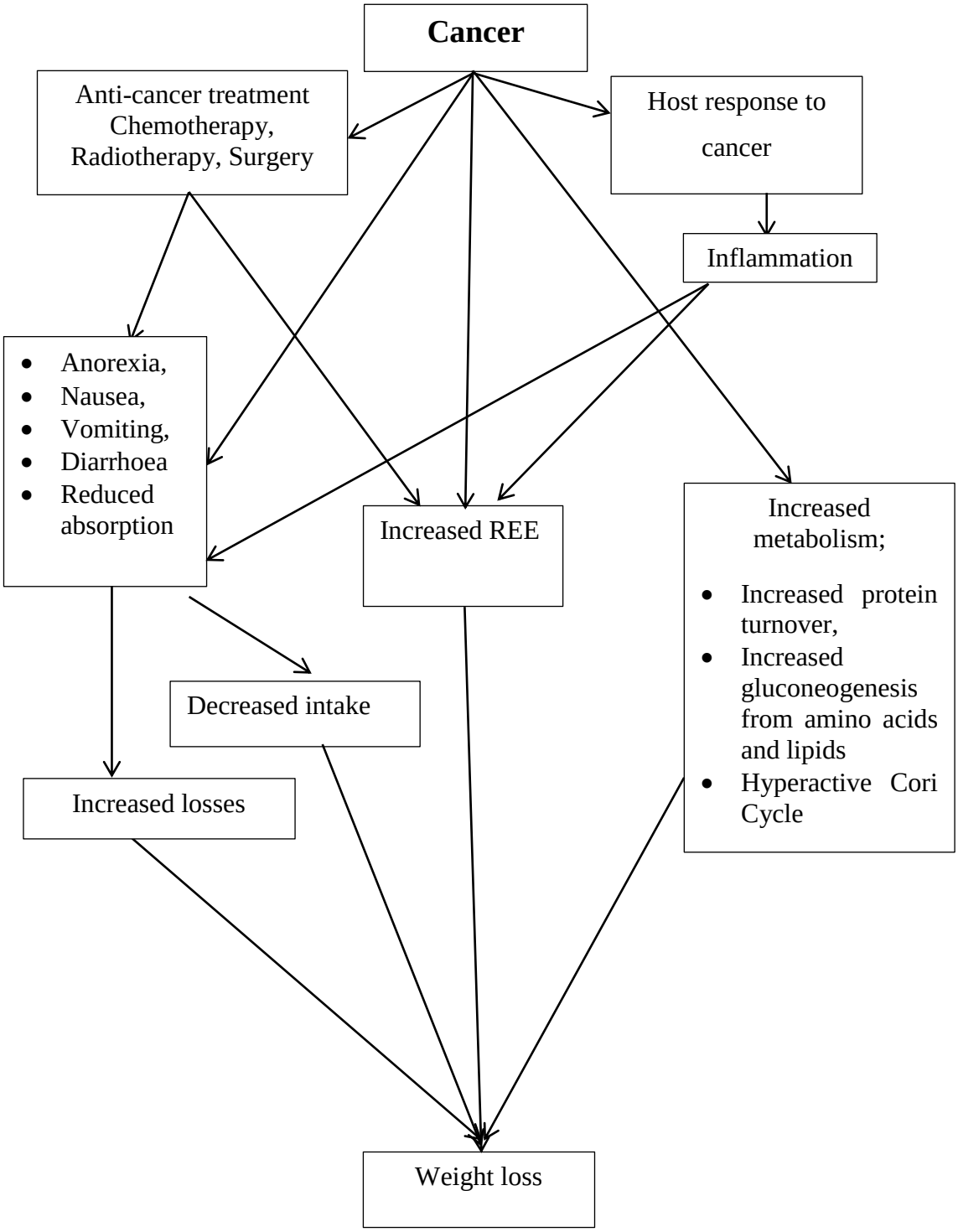


Figure 1.2 Multifactorial causes of cancer undernutrition. Cancer related undernutrition results from the combinations of multiple factors caused by the cancer it self, the treatments, and the host response to cancer and treatments.

1.4.1 Direct effects of tumour on undernutrition

Metabolic disturbances, caused by the tumour and the host response to treatments involving many organs causing a catabolic state and eventually leading to cachexia, are commonly reported contributors to the nutritional deterioration of cancer patients. The catabolic state or pre-cachexia is characterised by a breakdown of tissue and compounds caused by a body's response to stress, trauma, starvation and infection and it is define as weight loss >5%, anorexia and metabolic changes (Radbruch et al. 2010). Cachexia is a more advanced catabolic state characterised by wasting of lean tissue, muscle atrophy, inflammation and fatigue associated with significant changes in macronutrient metabolism for a prolonged time, often occurring in patients with advanced disease (Fearon et al. 2011).

Cancer cachexia causes the host production of catabolic mediators and inflammatory markers. However, the inflammatory response is not exclusively related to cachexia but can also be induced by infections (Prat et al. 2008; Stryjewski et al. 2005) and chemotherapy (Ek et al. 2001). The acute phase- protein response (APR) aims to prevent further tissue damage by initiating the repair process and isolating and removing the pathogen. In response to the pro- inflammatory cytokines (interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor (TNFα), the synthesis of APPs is stimulated in the liver (C- reactive proteins and mannose binding proteins) (Baumann and Gauldie 1994). This causes increased metabolism and weight loss (Falconer et al. 1994; Staal-van den et al. 1995) and is associated with poor prognosis in cancer patients with advanced disease (Blay et al. 1992). Cachexia is also mediated by circulating tumour-derived factors synthesised by the cancer itself which can cause breakdown of the host tissue (Norton et al. 1985). Examples of this include the proteolysis-inducing factor (PIF), which induces muscle wasting, (Cariuk et al. 1997) and the lipid mobilising factor (LMF), which induces mobilisation of adipose tissue (Bing et al. 2002).

There is strong evidence of cancer causing hyper-metabolism, increased protein turnover and gluconeogenesis in adults (Heber et al. 1992; Hyltander et al. 1991a). In a healthy and fed subject, the preferred substrate for energy metabolism is glucose. During the fasting state, visceral protein and muscle amino acids can be utilised as precursors of gluconeogenesis. When the body is in a fed state, protein catabolism

decreases and functional tissue is preserved. This preservation mechanism is altered in cachectic patients where the protein turnover is very rapid and amino acids are preferentially transported to the tumour to be used as source of energy. Furthermore, compared with a healthy subject, postprandial inhibition of amino acid uptake does not take place leading to the amino acids being used to produce ATP even in a fed state (Norton et al. 1980). Even though the energy requirement is met by glycolysis (Weber 1982; Weinhouse 1982), the cancer increases the hepatic production of glucose, lactate and amino acids from protein and fat tissue (Lundholm et al. 1981; Stein 1982). Glucose however is not taken up and metabolised from peripheral tissues due to the increased glucose intolerance and insulin resistance (Rofe et al. 1994). The utilisation of lipid and protein then leads to weight loss (McAndrew 1986). Furthermore, the rate of gluconeogenesis causes an increased requirement for gluconeogenetic enzymes which require the utilisation of amino acids in the liver for synthesis (Stein 1982).

The cachectic patient usually presents with oedema, anorexia, early satiety, anaemia and with severe weight loss (Fearon and Preston 1990). Cancer cachexia occurs in 30% to 80 % (DeWys et al. 1980; Kosacka et al. 2008) of total adult cancer patients, whereas the prevalence of cancer cachexia in paediatric cancer patients has not been precisely assessed. The complexity of cachexia and its definition make the diagnosis very difficult. The diagnosis of cachexia is generally based on both >5% weight loss and metabolic changes that are present. However, there is no specific definition of cachexia in children. Poor weight gain, or a shift of growth from expected trajectories, is also an important sign of nutrition inadequacy in children. Therefore, a weight loss of > 5% in children is more indicative of nutritional depletion in children than in adults and the definition of cachexia in childhood cancer patients should be made upon poor weight gain as well as weight loss >5%. However, only a few studies (Delbecque-Boussard et al. 1997; Schmid et al. 2005; Siimes et al. 1991; Siimes et al. 1991; Yu et al. 1994) have studied nutritional status in relation to inflammation in children with cancer.

A study by Siimes at al. (1999) measured the relation between TNFα concentration in relation to nutritional status (measured as muscle mass) in 12 children treated for

ALL during the first 16 weeks of treatments. They observed a high TNFα concentration at diagnosis followed by a gradual decrease to normal reference values at 16 weeks. A similar pattern of TNFα was observed in children with solid cancer undergoing chemotherapy but without the use of steroids, which excludes the normalising effect of steroids alone on TNFα release. The study did not show any correlation between nutritional status and TNFα. Elevated levels of inflammatory markers at diagnosis have also been reported elsewhere (Yu et al. 1994). Cytokine antagonists (soluble tumor necrosis factor receptor II and interleukin-1 receptor antagonist) have been studied in relation to nutritional status to investigate whether they had protective effects against undernutrition and hyper-metabolism. Their level was observed to be higher in children with high risk leukaemia (high white cell count) but did not relate to nutritional status (Schmid et al. 2005). In contrast, inflammatory markers were observed to be very low in paediatric ALL patients during the first ten weeks of treatments (Delbecque-Boussard et al. 1997).

From these findings inflammation seems a common feature at diagnosis and it decreases during treatments. However, the only study that investigated inflammation in relation to nutritional status failed to show any correlation (Siimes et al. 1991). Most of the studies had the limitation of investigating the relationship between inflammation and nutritional status in patients treated for ALL, which includes high doses of dexamethasone and prednisolone as part of their protocol. Steroids are known to reduce immune response and decrease cellular turnover (Pui and Jeha 2007) which are likely to have caused the decreased inflammatory markers during the first phase of treatments observed in the studies (Delbecque-Boussard et al. 1997). It is therefore very important to study the role of inflammation in order to assess the prevalence of cachexia in the development of undernutrition during cancer therapy.

The acute phase responses just described, (in both cachexia and catabolic state) causes raised REE which can contribute to weight loss and undernutrition. Several investigators (Bosaeus et al. 2001; Falconer et al. 1994; Hyltander et al. 1991a; Hyltander et al. 1991b; Moses et al. 2004; Nixon et al. 1988) have suggested that cancer is a hyper-metabolic disease causing elevated resting and non resting energy

expenditure in most adult patients affected by cancer. This continued negative energy balance leads to the development of undernutrition in cancer patients. However, even though there is unequivocal evidence to support the role of hyper-metabolism in adults, the evidence of increased REE in paediatric cancer patients is very limited.

Only few studies have investigated REE in paediatric cancer patients (Bond et al. 1992; den Broeder et al. 2001; Stallings et al. 1989), probably due to the methodological issues that this type of measurement implies. Measuring REE in children is very difficult. The most suitable method of measuring REE in a clinical setting is the computerised open circuit calorimeter, which has the advantage of being transported easily compared to the other techniques, such as the direct calorimetry. This technique is generally well accepted by the adult subjects, however, its use in sick children is challenging as children treated for a disease tend to be frightened by the use of the mask and they do not tolerate this measurement very well (Picton 1998). Furthermore, REE is intrinsically related to FFM therefore, measuring REE in this particularly cohort, must be done taking into consideration the possible lean body mass loss due to weight loss an the host response to cancer treatments.

The limited number of studies published suggests REE is related to tumour burden with a greater tumour load causing hyper-metabolism and a normalising effect of cancer therapy causing the REE to go back to expected values during cancer therapy (den Broeder et al. 2001; Schmid et al. 2005; Stallings et al. 1989; Vaisman et al. 1993). Increased REE was observed in a small cohort of nine newly diagnosed ALL patients compared to estimated REE for age gender and size. Remarkably, the observed increase in REE was found only in children with higher white cell count and organomegaly (high risk ALL) compared to the low risk ALL (Stallings et al. 1989). However, this study measured REE in relation to body weight without taking into account actual body composition. Since REE is intrinsically related to FFM, and body composition in this particularly cohort is affected by treatments, this methodology may have caused some error on the REE estimate. Similar results were also reported by den Broeder et al. (den Broeder et al. 2001) in 13 children with solid

tumours. They studied changes in REE corrected for differences (kcal/kg FFM) in body composition at three stages: diagnosis, during treatments and after two cycles of therapy. REE in relation to FFM was increased in 44% of patients at diagnosis, and then decreased by a mean of 12.6 % in all the patients during cancer treatment. After the two cycles of chemotherapy the REE for the treated group was no longer different to the expected REE.

Although all these studies suggest increased REE depending on tumour burden, the evidence to support hyper-metabolism in children remains inconclusive. A study (Green et al. 2008) conducted in a small cohort of ten children newly diagnosed with stage IV Neuroblastoma failed to observe any increased REE. The study recorded the REE at three points in time (diagnosis, after two courses of treatments and after surgery). Even though 50% of children where undernourished, the REE was not higher than the healthy matched control group during any of the three phases. Therefore, this study failed to show any increased REE at any stage of the disease in contrast to the other studies (den Broeder et al. 2001; Schmid et al. 2005; Stallings et al. 1989; Vaisman et al. 1993). However, this study did not measure FFM, and REE was compared against prediction values for healthy control matched for age, gender and weight. Therefore, similar to the Stallings et al. (1989), the methodology may have caused some error on the measurement of REE. More lack of evidence on increased REE in childhood cancer comes from Delbeque-Boussard and co-workers (1997) which assessed REE corrected for FFM at diagnosis, and during treatments. Although inflammation and increased REE has been observed by some authors at diagnosis (den Broeder et al. 2001; Schmid et al. 2005; Stallings et al. 1989; Vaisman et al. 1993), there is no evidence on the prolonged presence of hyper-metabolism and the occurrence of cachexia in children treated for cancer.

A possible confounder when assessing REE in cancer patients is the pro-inflammatory genotype. It has been shown that patient genetic makeup plays an essential role on response to inflammation which may contribute to the differences in the host response to cancer and cancer treatments. The risk of inflammation and consequent increased REE and cachexia is higher in genetically predisposed patients (Howell et al. 2002). Many studies in adult cancer patients, have shown that genetic

polymorphism for many pro-inflammatory cytokines such as IL1, IL6, IL8, TNFα (Broekhuizen et al. 2005; Jatoi et al. 2010; Tan and Fearon 2010; Zhang et al. 2007), can increase the susceptibility to cachexia. Nevertheless, genotypes that result in a decreased susceptibility to inflammation may have the reduced risk of developing cachexia (Tan and Fearon 2010). Therefore, the risk of increased REE is higher in specific cancer and in patients whose the genetic makeup predisposes them to an inflammatory status. This genetic predisposition may explain some of the contradictory results on the effect of cancer on REE previously discussed.

The literature is lacking to show evidence of raised REE during treatment for childhood cancer with the evidence of raised REE at diagnosis being limited. Comparison and interpretation of the studies reported (Bond et al. 1992; den Broeder et al. 2001; Green et al. 2008; Stallings et al. 1989), may be limited due to the heterogeneity of diagnoses studied (solid and ALL patients) even though all the studies used the same assessment method for measuring REE. In order to gain further knowledge on the energy metabolism in children treated for cancer, more research with large cohorts is now required, especially in children treated with protocols which do not include steroids. That would permit the stratification of patients by diagnosis and treatment protocols to specifically identify those groups of paediatric cancer patients at higher risk of hyper-metabolism REE and presumably at risk of poor nutritional status.

In addition to producing metabolic disturbances, the tumour mass may have direct detrimental effects on the host's food intake and absorption. Increased local pressure may occur in brain tumours and brain metastasis which lead to nausea and vomiting (Balducci and Hardy 1985). When the tumour mass is located in the head or neck, or in the GI tract, such as oesophageal, stomach and intestinal cancers, it may cause partial or total gut obstruction. This may lead to delayed digestion, nausea, vomiting, early satiety, intestinal atrophy, pain and difficulty in swallowing (Nitenberg and Raynard 2000). The delayed digestion may also cause longer transit and accumulation of gastrointestinal contents with excessive GI distension leading to early satiety and malabsorption (Nitenberg and Raynard 2000). Hence, physical

effects of solid may tumours exacerbate metabolic effects of cancer and cancer treatments.

1.4.2 Effects of treatment modality on undernutrition

Cancer treatments aim to cure the disease or slow down the tumour growth when a cure is not possible, while minimising symptoms and reducing the risk of recurrence. Each type of treatment modality and the host response to treatment may have specific effects on the development of undernutrition which have been described in this section. It is also important to consider that protocols which combine more treatment modalities e.g. chemo plus radiotherapy, may have a synergetic impact on side effects which ultimately result in greater effects on nutritional status.

1.4.2.1 Chemotherapy

Chemotherapy is a combination of drugs aiming to destroy fast dividing cells. Therefore, chemotherapy kills both rapidly dividing cancer cells and healthy cells which normally divide fast including haematopoietic cell, mucosal cells and hair follicles. As a consequence of this unselective cell damaging effect, chemotherapy has a range of side effects that depends on the type of drug used and may result in depression of the immune system , fatigue, gastrointestinal distress and hair loss (Pui and Jeha 2007).

Because of its damaging effects on the GI tract, chemotherapy can negatively affect the patient's nutritional status. Even though antiemetic drugs available are becoming more efficient, chemotherapy induced nausea and vomiting are still reported as causes of decreased food intake in children treated for cancer (Skolin et al. 2006). Furthermore, other drugs widely used in cancer patients, such as narcotic and antibiotics, can also cause nausea and vomiting (Grant and Kravits 2000) and quickly lead to dehydration and undernutrition.

Moreover, it has been widely described that chemotherapy causes changes in smell and taste perception in both adults and children which may further decrease food intake (DeWys 1974; DeWys and Walters 1975; Grant and Kravits 2000; Greene et al. 1994; Skolin et al. 2006). Learned food aversion is also often reported as a cause of decreased intake in children (Skolin et al. 2006) and adults (Grant and Kravits 2000). It develops in relation to foods that have become tasteless due to the changes

in taste perception, or towards food that were consumed close to chemotherapy followed by an unpleasant event such as nausea and/or vomiting (Skolin et al. 2006).

During the early years of life, a child develops eating behaviours which set the foundations for future eating habits and weight status (Savage et al. 2007). Therefore, as well as the direct detrimental effect on the nutrient intake during cancer therapy, it may negatively influence food choice and eating behaviours as adults. Hence, the learned food aversion has an even greater negative effect in children than in adults.

Furthermore, systemic chemotherapy causes mucositis, an inflammatory response on the epithelial cells of the gastrointestinal tract which causes lesions in various part of the GI tract. The dysfunctional mucosa causes pain with consequent decreased dietary intake and decreased nutrient absorption. Any of the gastrointestinal side effects of chemotherapy can therefore lead to acute or chronic loss and malabsorption of fluid as well as malabsorption of macronutrients and micronutrients and electrolytes. This exacerbates undernutrition and may cause dehydration (Donaldson 1982). A prolonged treatment with chemotherapy is likely to aggravate the side effects and it is likely to cause a greater risk of undernutrition (Grant and Kravits 2000).

Although the side effects of chemotherapy causing nutritional decline as described above are shared among many chemotherapeutic agents, this class of drugs is very vast and some treatments may have specific negative effects on nutritional status. For example vomiting, nausea and anorexia are common to most chemotherapy agents whereas taste and smell alteration have been reported in patients treated with carboplatin, doxorubicin, 5-fluorouracil or methotrexate, and mucositis in the treatment with antimetabolites (Grant and Kravits 2000). Therefore, those patients with treatment regimens which include a broad variety of chemotherapy drugs, are likely to experience a multiplicity of side effects, which place them at a higher risk of undernutrition.

1.4.2.2 Radiotherapy

Radiotherapy uses ionizing radiation to kill cancer cells. Radiotherapy side effects are usually limited to the area that is treated (Chan 2007). The detrimental effects on patients nutritional status varies depending on the length and dose of irradiation as well as the location of the irradiated area and the extent of body area treated. For example, radiotherapy in the abdominal pelvic (Donaldson 1977) and cervical area increase the risk of nutritional consequences (Piquet et al. 2002). Radiotherapy of the pelvic and abdomen area also damages the gastrointestinal mucosa causing mucositis leading to secretory and mixed diarrhoea. These gastrointestinal side effects, may lead to excess fluid loss, and electrolyte imbalance leading to dehydration. Furthermore, the damage to the intestinal lining causes impairment of carrier proteins responsible for the active transport of nutrient, decreased absorption of micro- and macronutrients leading to undernutrition (Donaldson 1982). A small percentage of patients treated with abdominal radiotherapy, develop chronic radiation enteropathy, a condition characterised by fistulas and gastrointestinal strictures leading to severe undernutrition. Irradiation of the head and neck also causes severe mucositis and pain resulting in decreased dietary intake and decreased nutrient absorption. This exacerbates dehydration and undernutrition (Piquet et al. 2002).

All the gastrointestinal and neural complications related to radiotherapy can lead to nutritional deficits and dehydration. In addition, cranial radiotherapy (CRT) can cause damage to the pituitary and hypothalamus (Borgstrom and Bolme 1988; Cicognani et al. 1988; Pomarede et al. 1984) been linked to the late onset of obesity in children treated for ALL. This topic will be discussed in more detail later (Section 1.5).

1.4.2.3 Surgery

It is well known that patients undergoing major surgery are at greater risk of undernutrition (Emery et al. 1999). Surgical trauma increases REE as a consequence of hyper-metabolism. This host response is activated to support inflammation and healing mechanisms to promote recovery. Furthermore it has been observed

(Dempsey et al. 1988) that after any type of major surgery, not just in cancer surgery, dietary intake is often remarkably reduced.

These features are generally short-term and they improve as recovery progresses. However it has been reported (Rivadeneira et al. 1998) in cancer patients who have undergone surgery of the gastrointestinal tract that they may have a prolonged decreased food intake and malabsorption. When the tumour mass is removed from the GI tract, food digestion and nutrient absorption can be impaired leading to those problems persistently. Fat absorption had been largely described to be inadequate after GI surgery (Lawrence et al. 1960; Walther et al. 1989) with consequent limitation in caloric intake and the absorption of fat soluble vitamins (Bozzetti et al. 2000). Furthermore, many other micronutrients with limited area for absorption in the GI tract, such as vitamin B_{12}, folic acid, iron and calcium are at risk of deficiency depending on the location of the resected area (Bozzetti et al. 2000).

The most common bowel malignancy in children is the non-Hodgkin lymphomas, however it only accounts for around 5% of total childhood cancers (Cancer Research UK 2012; Information Service Division Scotland 2012), with other gastro-intestinal malignancies even less common in children (Kliegman 2007) and therefore, the nutritional consequences of GI resection surgery are rarely observed in children compared to the adult population. Therefore, paediatric cancer patients treated with surgery as part of their treatment modality are likely to be hyper-metabolic short term after the surgical procedures, but less likely to be at risk of long term consequences. For this reason there is not any study focusing on the role of surgery alone in undernutrition during treatment for childhood cancer.

1.4.3 Meeting the energy requirements

The previous section explored the mechanisms by which cancer and its treatments can potentially disrupt the energy balance causing undernutrition. This section will review the evidence for changes in nutrient intake and the issues related to measuring dietary intake in children with cancer.

The association of poor dietary intake with undernutrition in children treated for cancer has not been extensively researched (Bond et al. 1992; Carter et al. 1983b; Delbecque-Boussard et al. 1997; Smith et al. 1991) and the few studies available in

the literature have used different methods to assess energy intake and determine the adequacy. Some studies (Bond et al. 1992; Carter et al. 1983b; Delbecque-Boussard et al. 1997; Smith et al. 1991) used healthy controls as a reference, whereas some others used the 80% of the recommended daily allowance (RDA) for healthy children as the cut off point for energy intake adequacy (Carter et al. 1983a; Smith et al. 1991) which make the interpretation of the results problematic.

The results from the studies conducted with a matched healthy control have shown a decreased energy intake especially at diagnosis. Delbecque-Boussard et al. (1997) compared dietary intake in 15 newly diagnosed children with ALL with a control group, by 24 h diet recall at diagnosis and at day 22, 36 and 71. They observed a significant lower energy intake at diagnosis compared to the control group; however this difference disappeared at day 36. This positive change in intake may be explained by steroid therapy, which is known to increase appetite (Loprinzi 1995). Similarly, Smith et al. (1991) observed that 27% of the total cohort treated for various types of cancer (n=62) at diagnosis consumed <80% of the energy requirements, compared to 1% of the matched control group.

In marked contrast Carter and co-workers (Carter et al. 1983b) reported the energy intake being around 80% of RDA and comparable to the healthy general population in 277 paediatric patients with several cancer types at diagnosis. The energy intake did not change after six months. This contrasting evidence may be caused by the methodological limitation of using 80% of RDA as criterion for adequacy. Bond et al. (1992) showed no evidence of decreased energy intake. Furthermore, they reported no differences in energy intake between both ALL and solid tumour patients to the control group during maintenance chemotherapy. However, the Bond et al. study (1992) was conducted in children in the maintenance phase, which is the last phase of treatment and involves different types of chemotherapy which may have accounted for the normal energy intake observed in the study.

Very interestingly, protein intake was found to be adequate when energy intake was found inadequate, which suggests that protein energy undernutrition in this cohort is not common (Carter et al. 1983, Delbecque-Boussard et al. 1997, Garcia et al. 1989). However, the protein intake was compared to the DRV (Dietary Reference Value)

for the healthy and this criterion to assess adequacy may be questioned since the specific protein requirement for children treated for cancer is unknown.

Assessing the energy status of a child treated for cancer is very challenging. Dietary assessment can be an extra burden for the family, and under-reporting is very common (Bandini et al. 1990). Furthermore, quantification of intake when a child is very sick after chemotherapy is very difficult. Additionally, there is no specific RDA or EAR (Estimated Average Requirements) for children treated for cancer and those for the healthy population are likely to be inappropriate. This is because the metabolic demand of cancer is unknown but is undoubtedly different to healthy children. Furthermore, DRV are generally based on an average level of physical activity for healthy children and it is likely that children treated for cancer are less active (Aznar et al. 2006; Sanford et al. 2008).

Due to the contrasting evidence in the literature and the major role that energy intake plays on the maintenance of energy balance, it is essential to understand how it is affected by cancer and its treatments. Furthermore, because cancer treatments vary during the course of the disease, longitudinal research is needed to assess what are the treatment phases at higher risk of undernutrition.

1.4.4 Consequences of paediatric cancer- related undernutrition

The consequences of undernutrition, during the treatments and the course of the disease are varied and some are shared with any child experiencing undernutrition such as growth and development impairment (Waterlow 1972), whereas some others are specific for the paediatric cancer patients. Undernutrition during cancer therapy has been shown to increase mortality (Lobato-Mendizabal et al. 1989; Sala et al. 2012), increase risk of morbidity (van Eys 1979; van Eys et al. 1980) and increase the risk of early relapse (Reilly et al. 1994). Although increased mortality has been extensively reported in relation to poor nutritional status in paediatric cancer in developing countries, (Lobato-Mendizabal et al. 1989; Mejia-Arangure et al. 1999; Viana et al. 1994; Sala et al. 2012) there is very limited evidence to support the increased mortality as a consequence of undernutrition in children with cancer in the western world (Donaldson et al. 1981; Lange et al. 2005).

A case control study (Mejia-Arangure et al. 1997) has reported increased mortality (2.6 times) in 17 ALL patients during the initial phase of treatment in undernourished patients compared with those well nourished. They also reported a significant increased risk of mortality with increased severity of undernutrition. Similarly, a prospective (five years) study, (Lobato-Mendizabal, Ruiz-Arguelles, and Marin-Lopez 1989) conducted in 43 paediatric patients newly diagnosed with ALL, reported that undernourished children had a worse outcome than well nourished children. Undernutrition at diagnosis was associated with shorter survival and lower tolerance to therapy. The survival after five years was 26% in undernourished children compared to 83% in well nourished children.

Although these studies showed a relationship between undernutrition and mortality, it is very hard to isolate nutritional status as an independent marker of clinical outcome. This is because none of the above studies accounted for the disease severity. Poor nutritional status may be a consequence of the severity of the disease hence the increased mortality and decreased event free survival, could be an effect of disease severity rather than undernutrition per se.

A retrospective study, (Lange et al. 2005) evaluated the association between the survival rate and being underweight (Body Mass Index (BMI) $\geq 10^{th}$ centile) in 768 American children affected by Acute Myeloid Leukaemia against outcome. This study is the only one which stratified the patients according to disease severity (blood cell count, cytogenetics). Treatment-related mortality (TRM) was significantly higher in undernourished patients. Therefore, this study has provided the first and only evidence on the poor prognosis as a result of undernutrition independent of disease severity.

Conversely, other studies showed that nutritional status at diagnosis was not associated with survival (Weir et al. 1998; Yaris et al. 2002). Weir et al. (1998) conducted a retrospective study based on the clinical notes of 1025 patients treated for ALL where nutritional status was measured by BMI SDS. The study failed to show any association between undernutrition and mortality. However, this study had the limitation of using weight related measurements, which are known to be affected by steroids and may have masked undernutrition. However, many other authors have

failed to show any prognostic effect of nutritional status (Pedrosa et al. 2000; Yaris et al. 2002) in paediatric cancer patients affected by both solid and haematological tumour. These contradictory findings for the increased risk of mortality in undernourished children are very hard to clarify. One possible explanation is the difficulty in isolating nutritional status as a cause of mortality independently of disease severity. Furthermore, nutritional status is very hard to assess in children treated for cancer because during cancer treatments weight can be affected by hydration status and tumour mass, masking weight loss (Pietsch and Ford 2000; Smith et al. 1991).

Although, the evidence for the detrimental effects of poor nutritional status on mortality in children treated for cancer is limited, its detrimental effect on time of relapse is well established (Donaldson et al. 1981; Reilly et al. 1994; Viana et al. 1994). Donaldson et al. (1981) conducted a retrospective analysis of the clinical records of 455 Australian paediatric oncology patients to investigate the role of nutritional status on relapse and survival. Nutritional status was assessed by comparing weight for height (W/H) to the median of the population for the same age and gender. They found a significant relationship between nutritional status at diagnosis and freedom from relapse in both localised and non localised solid tumours. Analogous results were reported by Reilly and co-workers (Reilly et al. 1994; Reilly et al. 1994) in a retrospective study in 78 children treated for ALL with poor nutritional status measured as W/H. Due to the retrospective nature of the study, it was not possible to establish the mechanisms responsible for the unfavourable outcome of the undernourished children. Similarly, a more recent prospective study (Sala et al. 2012) (n=2954) assessed the effect of undernutrition at diagnosis (measured by albumin, BMI, triceps skin fold (TSF) and mid upper arm circumference (MUAC)) on clinical outcome. After two years of treatments the malnourished children were more likely to stop cancer therapy and have a shorter event free survival.

There are several mechanisms believed to play a role in the increased mortality and morbidity risk caused by undernutrition in cancer. It has been observed that malnourished patients do not tolerate chemotherapy as well as well nourished

patients (Lobato-Mendizabal et al. 1989; Lobato-Mendizabal et al. 2003) and often have a shorter duration of chemotherapy with increased incidence of treatment toxicity (Andreyev et al. 1998). A study in 1555 adult GI cancer patients showed that undernourished patients (nutritional status measured as weight and weight loss) experienced more frequent and more severe chemotherapy toxicity and treatment delays than patients without weight loss. Furthermore, a multivariate analysis showed that those patients who had a significant weight loss had a 43% increased risk of death, and showed a better survival rate in association with better nutritional status. The authors concluded that the treatment delays and the reduced chemotherapy received as a consequence of undernutrition are the reasons for the increased mortality. However, similar to other studies (Lobato-Mendizabal et al. 1989; Mejia-Arangure et al. 1999; Viana et al. 1994) it is not clear if the weight loss was caused by disease severity hence the undernourished patients were simply more ill.

Undernutrition negatively affects haematopoiesis and immune function (Daly et al. 1979; DeWys et al. 1980) which causes increased incidence of infection and poor wound healing, therefore increasing the morbidity risk. A higher infection rate has also been reported in undernourished children treated for cancer compared to well nourished controls (van Eys 1979).

Although the negative effect of undernutrition in mortality from cancer in the industrialised word is still under debate, poor nutrition negatively impact outcome, increases morbidity and causes impairment of growth and development. Therefore, this review of the literature highlights the importance of early detection of poor nutritional status and the role of nutritional management in preventing detrimental consequences.

1.5 Obesity in paediatric cancer survivors

In the previous section, the pathophysiology of cancer-related undernutrition and its consequences has been widely described. This section will focus on the pathophysiology of obesity as a long term consequence of childhood cancer therapy. It is well documented that childhood cancer patients can become obese in later life (Dalton et al. 2003; Meacham et al. 2005; Oeffinger et al. 2003; Warner et al. 1995)

which is subsequently a recognised risk factor for diabetes, metabolic syndrome and cardio vascular disease (CVD) (Sinaiko et al. 1999). With the increased survival rate of childhood and adolescent oncology patients (Cancer Research UK 2012; Information Service Division Scotland 2012) the long term consequences of the disease and its treatments have become a serious consideration for cancer treatment and care, and it is now essential to address and identify risk factors for those modifiable outcomes.

Several studies have attempted to investigate the increased risk for obesity and its aetiology in cancer survivors (Dalton et al. 2003; Meacham et al. 2005; Oeffinger et al. 2003; Warner et al. 1995). The association between childhood cancer and later obesity has been mainly observed among ALL survivors (Nysom et al. 1999; Oeffinger et al. 2003; Razzouk et al. 2007; Schell et al. 1992) with little evidence for other types of childhood malignancies (Muller et al. 1998; Nysom et al. 1999). Since the increased risk of obesity has been primarily observed in ALL patients, the unique features of the treatments for this group have been a particular focus of research. Treatments for ALL differ from the other childhood cancers, mainly due the prophylactic use of CRT (which has been stopped in the more recent protocols), the use of high doses of steroids (dexamethasone and prednisolone) and for the longer course of chemotherapeutic treatments (three years for boys and two years for girls) compared to an average of the nine -twelve months for solid tumours.

A full understanding of the aetiology of obesity in ALL survivors would provide evidence for preventative clinical practice in this specific cohort. Many studies (Dalton et al. 2003; Meacham et al. 2005; Oeffinger et al. 2003; Warner et al. 1995) have investigated the relationship between treatments and characteristics of patients which lead to the late onset of obesity. Those studies identified non-modifiable characteristics such as age at diagnosis (Dalton et al. 2003; Reilly et al. 2000), and gender (Meacham et al. 2005; Oeffinger et al. 2003; Warner et al. 1995) , low BMI SDS (standard deviation score) at diagnosis (Reilly et al. 2000) and modifiable risk factors such as CRT and chemotherapy (Odame et al. 1994; Zee and Chen 1986). Conversely, some other authors (Mayer et al. 2000; Reilly et al. 2001; Warner et al.

1997b; Warner et al. 1998) have focused on the cause of energy imbalance which results in excess body weight following childhood cancer.

Targeting those high risk groups of patients is essential in order to prioritise intervention aiming to prevent obesity from the early stages. This section will focus on the evidence regarding the pathophysiology and the factors implicated for the increased risk of obesity in childhood cancer survivors.

1.5.1 Steroids therapy and the risk of obesity

Several investigators have focused on the role prednisolone and dexamethasone used in the treatment of ALL and their contribution to the increased risk of obesity in ALL patients. Steroids negatively impact growth and body composition (Ahmed et al. 2002; Groot-Loonen et al. 1996; Wallace et al. 2003) by impeding linear growth and stimulating weight gain (Ahmed et al. 2002). Further, prednisolone and dexamethasone are known to transiently increase appetite (Loprinzi 1995) and that altered appetite regulation would influence nutrient intake and lead to a positive energy balance. However, it is not clear whether this increase in body weight caused by steroids is a short term consequence or whether it persists after treatment. Hence, although steroid administration is known to potentially lead to excess body weight gain, the evidence to support this as the only cause of the late onset of obesity in ALL patients is still inconclusive.

Evidence to support the increased risk of obesity as a consequence of steroid therapy comes from a follow up study (Groot-Loonen et al. 1996) carried out in 92 ALL patients five to twelve years after treatments. The study reported a significantly greater long term increase in weight for height with dexamethasone treatment compared to those treated with equivalent dose of prednisolone (Groot-Loonen et al. 1996). Steroids inhibit growth by up-regulating somatostatin production from the hypothalamus, hence the authors argued that the inhibitory effect of steroids on growth hormone secretion (Giustina and Wehrenberg 1992) may be responsible for the observed long term weight gain after treatments, however the study did not test this hypothesis.

Further work which examined the late effects of treatment regimens on weight gain came from Van Dongen-Melman and co-workers (Van Dongen-Melman et al. 1995)

in a retrospective study after up to ten years of treatments. All the patients (n= 113 ALL survivors) were stratified according to treatments received (steroids vs. steroids +CRT). The study showed an increased prevalence of overweight that persisted over time. The prevalence of overweight after four years of treatment was comparable between the two groups (27% steroids only, 29% steroids + CRT, p=0.54). Therefore steroid therapy might be implicated in the increased prevalence of obesity in ALL survivors observed. The study also observed that dexamethasone caused the most significant weight gain immediately after therapy cessation. However, after four years, the differences between the two types of steroids disappeared and the highest prevalence of obesity (44%) was observed in those patients treated with a combination of the two steroids. Therefore, although the patients treated with dexamethasone may experience an immediate weight gain after treatments, the patients treated with prednisolone had the same risk of gaining weight long term. The Van Dongen-Melman and co-workers study (1995) had the advantage of a sample size that allowed comparison of irradiated vs. non irradiated patients which has not been possible in other studies (Odame et al. 1994; Zee and Chen 1986). However, the study (Van Dongen-Melman et al. 1995) did not explain the reason for the continuous weight gain after treatment cessation.

Only one study (Lustig et al. 2003) investigated the independent effects of steroid therapy on BMI in survivors of childhood cancers other than ALL. This study did not find any increased risk of developing obesity associated with steroid therapy on childhood brain tumour survivors. However, the study excluded patients on steroid treatment for longer than six months which may have influenced the results. Furthermore, the dose of steroids used in brain tumour is lower than in ALL, therefore comparison of data relating to ALL studies, where steroid therapy is also much longer, may not be appropriate.

In summary, the evidence suggests a detrimental effect of steroid therapy in childhood ALL on body composition and BMI. However, the mechanisms by which they cause long term weight gain are still not fully understood and there is no convincing evidence to support the solely role of those two chemotherapeutic drugs on the late onset of obesity in childhood ALL survivors. Therefore, the underlying

mechanisms for the late development of obesity in survivors of childhood cancer are still unclear and the increased risk of obesity observed in this patient group is likely to be multifactorial. This area of investigation needs to be explored further since steroids are widely used to treat ALL and to decrease intracranial pressure in brain tumour.

1.5.2 Energy balance

Several studies have focused on the disturbances of energy balance in childhood ALL as a risk factor for the late onset of obesity rather than treatments (Mayer et al. 2000; Reilly et al. 2001; Warner et al. 1997b; Warner et al. 1998). There is strong evidence to support the idea that children treated for ALL are in positive energy balance as consequence of increased dietary intake (Reilly et al. 2001), reduced energy expenditure (Reilly et al. 1998; Warner et al. 1995; Warner et al. 1997b; Warner et al. 1998) and reduced physical activity (PA) (Aznar et al. 2006; Jacob et al. 2007; Jansen et al. 2009; Sanford et al. 2008).

For example Reilly et al. (Reilly et al. 2001) investigated energy intake associated with steroid therapy. The maintenance phase thus was associated with a 20% increased in energy intake during the five day period on steroids compared to the off period, although there was a significant difference between dexamethasone and prednisolone. They also observed a significant increase in BMI SDS in the ALL group treated with steroids in maintenance, compared to reference data. The study did not find a significant difference between the two types of steroids used, however the study was only carried out up to two years post diagnosis and it is not possible to draw a conclusion on longer term effects of the drugs beyond this.

These findings are in contrast with the Wallace study (Wallace et al. 2003), where dexamethasone therapy was found to be more potent in causing weight gain than prednisolone at similar doses. Being important contributors to the weight gain observed in ALL patients, the different effects of those two steroids in energy balance are very important and must be explored further.

Similarly, another study (Jansen et al. 2009) reported increased energy intake in ALL patients (n=16). However, Jansten and co workers (2008) also compared the energy intake during the period on dexamethasone and off dexamethasone. Interestingly

they found a significant increased energy intake during dexamethasone compared to control (2,125.9 ± 476.0 kcal/d vs. 1,775.1 ± 426.1 Kcal/d respectively) and a significant lower energy intake during the phase off dexamethasone compared to control (1,305.0 ± 249.4 Kcal/d vs. 1,775.1 ± 426.1 Kcal/d respectively). The increased energy intake during the period on dexamethasone observed in those studies may contribute to the weight gain observed in ALL patients. However, other studies did not show any increased energy intake associated with ALL treatments in the remission phase (Bond et al. 1992; Mayer et al. 2000). Those contradictory findings are difficult to reconcile but it may be that different treatment phases for ALL cause differences in energy intake.

Some studies (Reilly et al. 1998; Warner et al. 1998) offer convincing evidence to support a decreased level of TEE in this cohort. For example, Warner and co-workers (Warner et al. 1998) measured total daily energy expenditure by indirect calorimetry in 88 long term survivors of ALL at least 1.5 years from cessation of treatments and compared this cohort to 21 children previously treated for other malignancies and to healthy siblings as controls. The study reported a significant lower total energy expenditure (TEE) in all ALL survivors (TEE= 150 Kj·Kg·d) compared to other malignancies (TEE= 207 Kj·Kg·d) and control (TEE=185 Kj·Kg·d). The presence of decreased energy expenditure is also supported by the work of Reilly and colleagues (Reilly et al. 1998) who studied 20 patients treated for ALL without CRT and control subjects at mean 4.5 years after diagnosis. Energy expenditure was calculated using the doubly labelled water method and, when compared to the control they found a much lower total energy expenditure and energy intake (mean differences of 286 Kcal/d for TEE, 76 Kcal/d for REE and 238 Kcal/d for energy intake). The decreased energy expenditure considered in relation to the length of ALL treatments (two years for girls and three years for boy) would suggests that the energy excess experienced by these patients could indeed result in the consequent onset of obesity.

Evidence suggests that the positive energy balance observed in ALL cancer patients survivors may be also accounted for by reduced physical activity. The accurate assessment of PA however is very difficult because of its methodological limitation.

There are two types of methods to assess physical activity, the subjective, which includes questionnaires and interviews, and the objective, which involves measurements of physiological or biomedical parameters by instruments such as a pedometer or an accelerometer (Corder et al. 2008). The subjective methods rely on the ability to accurately recall physical activity which may also be influenced by the judgment of the reporter or interviewer (Sallis 1991). Furthermore, the estimation of energy expenditure from the subjective methods rely on equations based on adults and may do not apply to the children (Sallis 1991). Consequently questionnaires are not very accurate and do not provide a good measurement of PA in children. However, the accelerometer has been indicated as one of the best methods for assessing free-living physical activity and strong validity has been observed in laboratory conditions (Freedson et al. 1998; Nichols et al. 1999; Trost et al. 1998; Trost et al. 2000; Welk et al. 2003). Nevertheless, this method is only able to record physical activity on a vertical axis and physical activities on a horizontal axis such as cycling are likely to be under recorded (Cooper et al. 2005). Furthermore the accuracy is strictly dependent on the length of measurement with four to five days being suggested as the minimum required to guarantee accuracy (Trost et al. 2000) and this would require a high level of subject cooperation. The high participant cooperation and the time length required to carry out the measurements may account for the limited sample size and limited numbers of studies aiming to assess PA in children treated for cancer.

The studies available in the literature on the level of physical activity as a component of TEE during treatments for childhood cancer, were conducted using both the accelerometer (Aznar et al. 2006; Jacob et al. 2007; Jansen et al. 2009; Sanford et al. 2008) and numeric rating scale (Jacob et al. 2007). The unequivocal evidence from these studies supports reduced PA during treatment for childhood cancer (Aznar et al. 2006; Jacob et al. 2007; Jansen et al. 2009; Sanford et al. 2008).

For example, a study (Aznar et al. 2006) showed a significantly lower PA assessed by accelerometer in children (n=7) undergoing maintenance therapy for ALL (320±107 min/ week) compared to control (506±175 min/ week). The presence of reduced PA in ALL patients was also observed by Jansen and co-workers (2009)

who studied 16 ALL patients in maintenance treatment and 17 matched controls. When compared to control they noted a significantly reduced physical activity related with the treatment phase. PA was observed to be lower than control (30.0 ± 3.9 vs. 40.0 ± 6.0 kcal/kg/day) during the days on dexamethasone compared to the days off the drug, when, PA did not differ from the control group. The difference in PA depending on the therapy phase has also been observed elsewhere (Sanford et al. 2008). This finding would suggest a particularly increased risk for sedentary behaviour during dexamethasone; hence this phase of treatment should be a potential target for intervention aiming to increase PA during cancer therapy.

A similarly reduced PA was also observed in paediatric patients treated for other types of malignancies (Jacob et al. 2007, Winter et al. 2009). For example, Winter and co-workers (2009) showed a decreased level of PA in 80 children treated for cancer compared to 45 healthy controls using the accelerometer method. Furthermore, they showed differences in PA during hospital stays compared to the days at home. Children treated for cancer had 77% lower physical activity compared to the healthy control during the hospital stay, whereas, the physical activity was higher during the days at home, but was still lower compared to the control by 60%. Those findings suggest that children treated for cancer are at risk of reduced PA and, remarkably, those children with longer hospital stays are at even higher risk of reduced physical activity. PA affects various aspects of development and it must be considered as an essential part of a child's life. Therefore the reduced PA observed in this patient group must be regarded not only in relation to the energy balance homeostasis but also to the achievement of normal growth and development.

In summary, the evidence suggests increased energy intake (Reilly et al. 2001) , reduced physical activity during treatments (Jansen et al. 2009, Jacob et al. 2007, Jacob et al. 2007, Aznar et al. 2006) and reduced energy expenditure implicated on the late onset of obesity. However, it does not explain the underlying causes for the reduced physical activity in ALL survivors. The differences in energy expenditure among patients treated with steroids suggest the implication of this class of drug however the exact mechanism are still unknown. Moreover, some authors (Reilly 2009) have suggested the reduction of physical activity and increased sedentary

behaviour as a psychosocial response to ALL treatment. However, the discussion of the psychological aspects of cancer treatments goes beyond the purpose of this paper.

1.5.3 Early Adiposity Rebound

A possible factor that may play an important physiological role for the onset of obesity following childhood cancer therapy is the early adiposity rebound (AR). The adiposity rebound is a phenomenon that generally occurs between the age of five and six where, after having reached the minimum body fatness (nadir) the BMI and fat mass (FM) increase again into adulthood (Rolland-Cachera et al. 1984). The occurrence of AR before the age of four is very rare and it has been widely reported that children undergoing an early adiposity rebound are at higher risk of developing obesity in later life (Gasser et al. 1995; Rolland-Cachera et al. 1984; Rolland-Cachera et al. 1987; Williams et al. 1999). Since the average age at diagnosis for ALL is around three years of age, it has been hypothesised that the start of childhood ALL treatments causes AR to start early. This would cause a shift in the adiposity rebound trajectories and lead to the excess fat gain observed in this cohort (Reilly et al. 2001b). To date, only one study (Reilly et al. 2001b) was performed on children treated for ALL to investigate whether they experience early AR. The authors studied the timing of AR in 35 boys and 35 girls who survived ALL with a mean age at diagnosis of 30 months. The study showed that 42.6 % of ALL survivors had AR at the age of three and 80.9 % at the age of four in contrast to 4.5% at age of three and 21.2 at age of four in the control group. Interestingly, these findings confirm that AR occurred significantly earlier in patients treated for ALL compared to the matched healthy group and that the degree of positive energy balance was enough to cause early AR. Therefore, these findings show that timing of treatments of ALL can be an independent risk factor for the late onset of obesity.

Early AR may be a possible explanation for the increased risk of obesity in children diagnosed before four years of age. However, the underlying mechanism causing early AR in children treated for ALL is still poorly understood. Disrupted appetite regulation could be an important contributor to early adiposity rebound in ALL survivors. Subjects who experience large FM losses tend to have a consequent energy compensation mechanism (hyperphagia) with a consequent excess body

weight regain (weight over-shooting) (Dulloo et al. 2012). This phenomenon is illustrated in Figure 1.3 and may be applied to children treated for ALL in maintenance where steroids are taken in pulses. During maintenance therapy, they experience alternate phases of low energy intake when off steroids and high energy intake when on steroids (Jansen et al. 2009). This may cause the FM losses during the off steroids period as a consequence of chemotherapy, followed by hyperphagia during the steroid period, which possibly causes fat overshooting and might lead to excess body weight gain observed in ALL survivors.

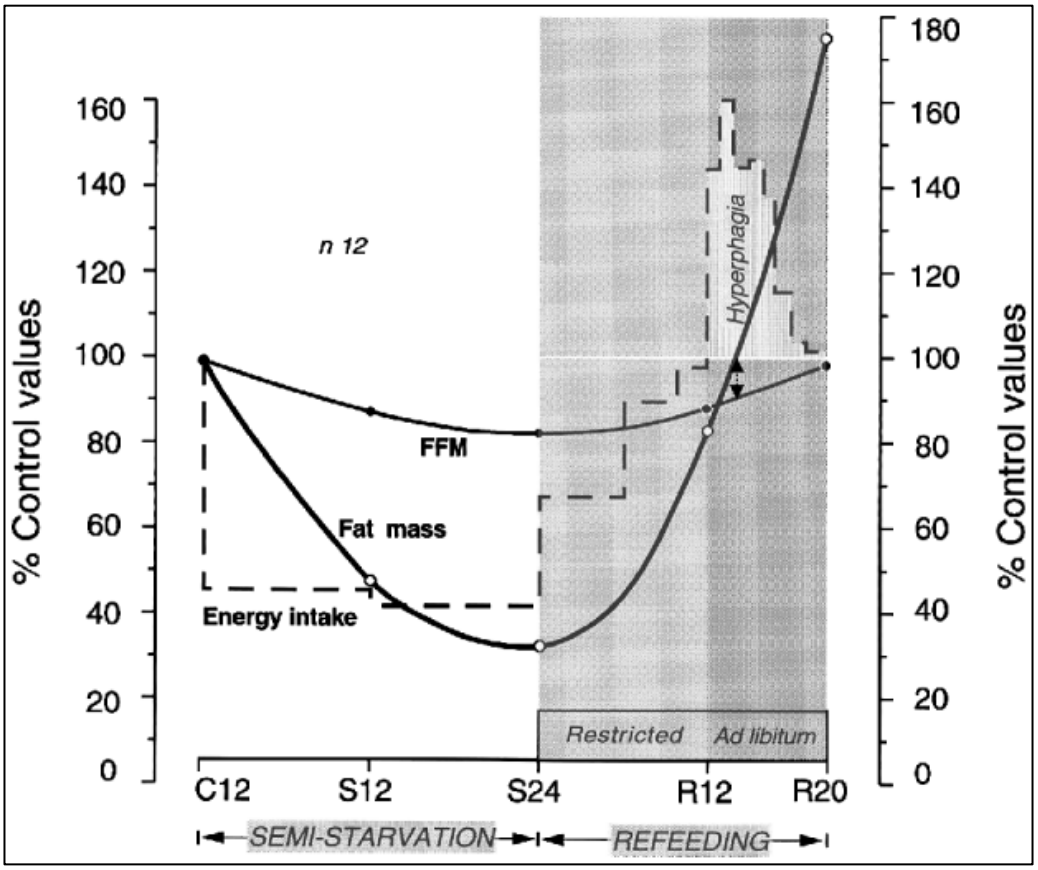


Figure 1.3 Pattern of changes in energy intake, body fat (FM) and fat free mass (FFM) (Dulloo et al. 2012).

However, to date, there is no data to suggest that this model (Dulloo et al. 2012) can be applied to ALL patients. Therefore in the future prospective studies should aim to investigate adiposity rebound in children treated with chemotherapy and CRT before the expected age of AR and in relation to appetite regulation and FM overshooting as a consequence of starvation and hyperphagia.

1.5.4 Cranial irradiation

Evidence suggests a detrimental role of CRT on BMI and excess weight gain in survivors of ALL with an increased risk at higher radiation doses (Groot-Loonen et al. 1996; Odame et al. 1994; Oeffinger et al. 2003) and according to gender, with females being at higher risk (Oeffinger et al. 2003). A large (n= 1765) retrospective study (Oeffinger et al. 2003) compared a cohort of childhood ALL to a sibling control group (n=2565). They investigated whether excess weight gain was associated with different doses of cranial radiotherapy or a chemotherapeutic agent. Furthermore, they assessed if age at diagnosis and gender affected the risk of obesity. They observed a significantly increased prevalence of excess body weight and obesity among ALL survivors group who received higher doses of CRT (≥20 Gy) when compared with siblings. However, the study did not find any association of obesity with any chemotherapeutic agent alone or for those patients who received chemotherapy and CRT of 10 to 19.9 Gy. Females treated with chemotherapy and CRT ≥ 20 Gy were found to be a greater risk of being overweight or obese when compared to the male cohort (OR 2.59, 1.86 respectively). Furthermore this risk was further increased by age at diagnosis with the greater risk for those female diagnosed at age of zero to four (OR 3.81) (Oeffinger et al. 2003).

Further work to support the relationship between CRT and the late onset of obesity comes from a retrospective analysis (Odame et al. 1994) of the frequency and trend of weight gain in 40 survivors of childhood ALL in relation to CRT at a dose of 1800 Gy against matched oncology patients who received chemotherapy but not radiotherapy. A significant weight gain was observed at four years with 57% of girls (mean BMI SDS 2.36 ; SD 1.2) and 21% of boys (mean BMI SDS 1.13 ;SD 1.2) being obese (classified as SDS >2).

More recent studies used the DEXA method (Dual Energy X-ray absorptiometry) to evaluate body composition as a gold standard for evaluating adiposity in ALL survivors (Jarfelt et al. 2005; Nysom et al. 1999; van Beek et al. 2006; Warner et al. 2002). These studies showed an increased percentage of body fat in ALL survivors who were treated with CRT compared with those not receiving CRT, even when the BMI values were similar between the two groups (Jarfelt et al. 2005; Nysom et al. 1999; Warner et al. 2002). These finding suggests a detrimental effect of CRT on

body composition and would advocate that the increased risk of obesity reported by the previous study may be even higher. However, other studies did not observe any increased risk of obesity in ALL in relation to CRT and failed to report an increased risk according to age at diagnosis and gender (Dalton et al. 2003; Razzouk et al. 2007; Van Dongen-Melman et al. 1995). The reasons for this inconsistency are not clear. Although, the use of BMI is common in clinical practice, its ability to measure body fatness in children with cancer may be questioned.

Only one study (Gurney et al. 2003) evaluated the BMI changes in response to CRT in survivors of brain tumours. They did not identify any effect of treatments on having BMI >30 or more in the 921 patients analysed in remission when compared to control. The female group with an early age at diagnosis (<4 years) however was associated with the risk of obesity. Furthermore, the risk of obesity among the entire female cohort was increased two to three fold when they were treated with CRT, which seems to indicate an effect of gender.

There appears to be a consensus on the detrimental role of cranial radiotherapy on the development of obesity in ALL survivors. Analysis of body composition in ALL survivors showed that patients treated with protocols which included CRT have increased body FM compared to the non CRT groups even at similar BMI values. Female ALL survivors are especially at increased risk of excessive FM in later life. However, the majority of the studies above aiming to research changes in body composition as a consequence of CRT have the limitation of a small sample size. Furthermore, the prevalence of obesity in ALL survivors has been reported to increase significantly even in patients that have been not been treated with CRT (Dalton et al. 2003; Razzouk et al. 2007; Van Dongen-Melman et al. 1995). This evidence suggests the involvement of other factors on the development of obesity. This is significant when considering that most recent protocols no longer include prophylactic CRT.

One possible reason for the observed weight gain following extensive cranial irradiation and tumour excision is hypothalamic-pituitary axis damage. The hypothalamus and hypothalamus-pituitary axis regulates many physiological processes including food intake. When the hypothalamus is structurally damaged a

condition defined as hypotalamic obesity can occur. Muller et al. (Muller et al. 2004) showed an increased risk of obesity in cranyopharyngioma (benign brain tumour) survivors in a longitudinal retrospective study from birth to median 6.2 years post diagnosis. They reported a significantly higher BMI at diagnosis and during follow up in the craniopharyngioma group with hypothalamic involvement (n=49). One of the possible consequences of hypothalamic-pituitary axis damage responsible for the increased risk of obesity, is the growth hormone deficiency (GHD), with increased risk observed with higher and longer doses of CRT (Borgstrom and Bolme 1988; Cicognani et al. 1988; Pomarede et al. 1984). However, some studies did not show any relation between CRT and GHD (Birkebaek et al. 1998; Gurney et al. 2006)) and reported an increased risk also in ALL survivors who were treated with chemotherapy alone. This evidence suggests a possible implication of other factors such as chemotherapy, other than hypothalamic- pituitary axis damage alone on the development of GHD and obesity in childhood survivors.

Another possible consequence of CRT implicated in weight gain, is the damage of mechanisms that control body weight. The body controls weight homeostasis by an intricate series of pathways which regulate food intake, energy expenditure and fat deposition (Hochberg and Hochberg 2010). Damage to key anorexogenic (e.g pro-opiomelanincortin (POMC)), orexigenic signalling neurones (eg. Agouti Related Peptide (AgRP) and Neuropetide Y (NPY) and/or Leptin insensitivity, as consequence of head cancer and CRT, has been reported as the possible cause of obesity in this cohort (Hochberg and Hochberg 2010). For example, Brennan and co-workers (1999) described that CRT causes damage to the Leptin receptor in the hypothalamus which disrupts the Leptin signal and ultimately results in obesity. In this study they assessed BMI and Leptin concentration in 32 survivors of ALL previously treated with CRT in comparison to 35 matched healthy controls. BMI and FM were not significantly different between the two groups, however, lean body mass was significantly decreased and Leptin was significantly increased in the ALL survivors, which may have occurred as a consequence of hypothalamic damage or GH deficiency. The Brennan et al. (1999) study has provided the first evidence to suggest the presence of damage involving other pathways implicated in food intake regulation rather than GHD alone following CRT.

Further evidence to support the potential damage to the Leptin pathway as a consequence of CRT in ALL survivors, comes from a later study (Ross et al. 2004). Because the development of obesity after CRT in ALL patients has been shown to be inconsistent, the authors suggested a polymorphism in the LEPR gene as contributor of this discrepancy. The study showed that LEPR polymorphism influenced the predisposition to obesity in female ALL but not in males at similar genotype distribution. These findings would explain the increase risk for later obesity in the female population treated for ALL previously described (Odame et al. 1994; Oeffinger et al. 2003). However, those findings are still preliminary and further research is needed on LEPR polymorphism to clarify the presence of a gender predisposition. In conclusion, GHD and Leptin insensitivity are believed to be the possible causes for the late development of obesity in this cohort and the reasons for GHD in non irradiated patients are still unknown.

In summary, obesity as a long term consequence in children treated for cancer is well documented and, with the increased survival rate, prevention of this should be a consideration during and after treatment. It is evident from this review that a number of mechanisms lead to a positive energy balances in this cohort. Reduced PA, increased appetite and the damage to the nervous system regulating appetite and growth are now well identified mechanisms to contribute to this imbalance. It is well known that prevention of obesity is more achievable than treatments and it is feasible in children (Dietz 1998). Therefore, during the clinical management of the disease, excess weight gain should be monitored closely and raise concern as there should be an attempt to treat and prevent excess body weight during ALL treatment. For example, it might be prudent to encourage PA whenever possible. However, even though the mechanisms leading to excess body weight have been identified, the literature lacks intervention studies, aiming to modify patients' behaviour or treatment regimens in order to prevent the late onset of obesity. Therefore future research should focus on intervention studies preferably multicentre, randomised controlled trials to understand how to prevent this childhood ALL sequela. Considering the limited number of new referrals for childhood cancer to each hospital per year, a multicentre study would be essential to ensure an appropriate sample size. Furthermore, random allocation to the intervention and non intervention

groups would ensure the exclusion of differences between the two groups and would reduce the bias (Sibbald and Roland 1998)

1.5.5 Consequences of paediatric cancer- related obesity

Only two studies have investigated the prognostic effects of excess body weight and obesity in paediatric oncology patients (Butturini et al. 2007; Lange et al. 2005) and they reported an increased mortality rate and an increased risk of relapse among obese children.

The first retrospective study (Lange et al. 2005) evaluated the association between survival rate and obesity (BMI ≥ 95% percentile) in 768 American children affected by Acute Myeloid Leukaemia against outcome. Treatment-related mortality (TRM) after the second course of chemotherapy was significantly higher in the overweight compared to the normal weight group (Hazard Ratio 3.49). The authors hypothesised that obese patients were receiving too much chemotherapy leading to chemotherapy toxicity and death. However, the analyses of data concerning neutrophil recovery and course duration, which are an index of chemotherapy toxicity, suggested that obese patients were receiving the right amount of chemotherapy. This study has provided the first evidence to suggest that obesity during cancer therapy is associated with increased mortality.

The second study (Butturini et al. 2007) retrospectively analysed data from 4260 patients diagnosed with ALL. The cohort consisted of 342 (8%) obese patients (BMI ≥ 95^{th} percentile) and 3.971 non obese patients (92%). They reported an independent negative effect of obesity on outcome when compared to normal weight patients. The five years event free survival (EFS) rate was significantly lower for the obese group (72% ± 2%) compared to the non obese group (77%± 0.6%). This study showed an increased risk of relapse but they did not assess the risk of increased mortality. Contrary to the Lange et al. study (2005), they believed obese patients where at higher risk of relapse compared to the normal weight patients because of an inadequate chemotherapy dose since it is calculated based on body surface area. However, the outcome was independent of the chemotherapy dose.

This limited data is also mirrored by adult studies. The obesity-related increased risk of relapse has also been reported in adults affected by ALL, (Butturini, Vignetti and

Gibbotti 2005), colorectal cancer (Meyerhardt et al. 2004) and breast cancer (Colleoni et al. 2005) and the obesity-related increased risk of treatment induced mortality has been reported in adult patients affected by acute myelogenous leukaemia (Meloni et al. 2001)

These two studies (Butturini et al. 2007; Lange et al. 2005) have the limitation of assessing obesity based on BMI centile which may not be the best method to assess adiposity in children with chronic disease since it tends to underestimate FM (Warner et al. 1997a). Moreover, it is not possible to conclude what the causes of the observed increased mortality are, and it is not known whether those detrimental effects are caused by obesity per se, or if they are a consequence of factors associated with obesity, such as unhealthy diet and lack of exercise.

The mechanisms causing increased mortality and morbidity in obese cancer patients are still poorly understood. Some authors suggested that obese patients receive less chemotherapy than needed (Bastarrachea et al. 1994; Georgiadis et al. 1995; Meyerhardt et al. 2004) which are in contrast with the Butturini et al. (2007) and the Lange et al. (2005) results. This inconsistency is hard to explain but possibly due to different diagnostic groups analysed and the different type of chemotherapeutic drugs used. Some authors propose a more complex interaction between obesity and chemotherapy (Brakenhielm et al. 2004; Fukuhara et al. 2005). Adypokines, growth factors and lymphokines produced by the adipose tissue or in response to the metabolic syndrome may alter cancer therapy effects and increase toxicity (Brakenhielm et al. 2004; Fukuhara et al. 2005; Onuma et al. 2003). Leptin and growth factor increase cancer growth (Onuma et al. 2003) and tumour necrosis factor (TNF) and IL-8 and IL6 increase inflammation, oxidation and increase angiogenesis and tumour growth (Brakenhielm et al. 2004; Fukuhara et al. 2005)

In this chapter the consequences of obesity during cancer treatments and after recovery were extensively discussed. However, evidence for the detrimental effects of obesity is very limited. The published studies suggest an increased risk of mortality and morbidity which has also been reported in adults patients. Furthermore, the long term consequences of obesity, such as increased risk of CVD later in life cannot be ignored. Therefore, issues relating to over and undernutrion

paediatric cancer patients needs effective management to reduce possible nutritional consequences

1.6 Nutritional management in paediatric oncology patients

As previously discussed, for many childhood cancer patients, the progression of the disease and the start of cancer treatments can bias the nutritional status towards malnourishment (under or overnutrition) with many detrimental consequences (Donaldson et al. 1981; Mejia-Arangure et al. 1999; Rickard et al. 1983; Viana et al. 1994). Hence, identification of patients at nutritional risk from diagnosis and throughout treatment is essential.

Early identification of high risk or undernourished patients would allow close nutritional monitoring and prompt nutritional therapy. This would help to prevent the decline of nutritional status, support growth and development. Additionally, a rapid identification of those patients at high risk of becoming overweight and obese would allow a preventative intervention targeting potentially modifiable risk factors, such as diet and sedentary life-style to be initiated.

Nutritional management should therefore be an essential part of paediatric cancer treatment. The ESPGHAN committee on nutrition has highlighted substantial deficits in nutritional management in paediatric hospitals across Europe (Agostoni et al. 2005). The implementation of nutrition support teams in paediatric units has therefore been suggested. Amongst the various recommendations from the ESPGHAN meeting, of relevance to the current research study, is the urgent need for screening of nutritional risks, the identification of patients who requires nutrition support (NS) and the provision of adequate nutritional management.

From an audit conducted in 2003 within the 'Royal Hospital of Sick Children, Edinburgh' (RHSC) (Holt 2003), it emerged that oncology patients were not having their height and weight monitored and consequently were not being referred appropriately for dietetic intervention. Only 30% of the patients in the audit had growth chart completed and patients had a weight loss greater than 5% before NS initiation. It was apparent that it was unclear whose role it was to conduct the nutritional screening. This evidence underlines the urgent need for a proper way of

assessing nutritional risk in children undergoing cancer treatments. An appropriate nutritional screening tool should be able to predict outcome due to factors relating to nutrition and to estimate the likelihood of adequate nutritional intervention on affecting the nutritional outcome in this particular group of patients.

A general nutritional management pathway is adopted in the adult health care setting is shown in Figure 1.4 (Elia 2005). Its applicability in the paediatric scenario however, is difficult for many reasons. The main difficulties identified are the lack of a specifically designed screening tool for paediatric cancer patients and the limitations of the nutritional assessments available for assessing nutritional status in this cohort. These issues will be explored in this chapter.

Figure 1.4 General nutritional management pathways (Elia 2005)

1.6.1 Nutritional screening

The first step for the management of undernutrition is the identification of undernourished patients or those at risk of developing undernutrition. Nutritional screening should aim to detect those patients who are malnourished or at risk of undernutrition so that an appropriate course of action can be taken. Nutritional screening is generally carried out by those members of nursing or medical staff at first contact with the patient. Any tool used for screening should be quick and easy to complete in order to allow for immediate action and subsequent monitoring.

The European Society of Enteral and Parenteral Nutrition (ESPEN) recommend the Malnutrition Universal Screening Tool (MUST) for the screening of adults, in both community and health care setting (Kondrup et al. 2003a). However, to date , there are few screening tools for assessing the risk of undernutrition in general paediatrics;

the Subjective Global Nutritional Assessment (SGNA)(Secker and Jeejeebhoy 2007), the Screening Tool for Assessment of Malnutrition in Paediatrics (STAMP) (McCarthy et al. 2008) and the Paediatric Yorkhill Malnutrition Score (PYMS)(Gerasimidis et al. 2010). Nevertheless, a validated screening tool for paediatric oncology patients is not yet available and the lack of a specific nutritional screening tool is a well recognised limiting factor for improving nutritional care in hospitalised children, including childhood cancer patients (Kondrup et al. 2003a).

The Subjective Global Nutritional Assessment (SGNA) (Secker and Jeejeebhoy 2007), is an adaptation of a previously designed adult nutritional assessment tool (Subjective Global Assessment) (Baker et al. 1982). It was validated (Secker and Jeejeebhoy 2007) in a prospective study that followed children having thoracic and abdominal surgery. The SGNA includes the child's height, weight history, the family weight and height, dietary intake, type, frequency and duration of gastrointestinal symptoms, functional capacity muscle and FM wasting, oedema as well as metabolic demands of the disease. Its use was shown to correlate with the markers of nutritional status examined in the study (height (H), weight (W), TSF, MUAC, % of ideal body weight, handgrip strength, albumin transferrin, haemoglobin and white cells). The authors therefore concluded that this new tool was a valid means to assess those at higher risk of later undernutrition. However, this tool was not designed or validated for childhood cancer patients. Moreover, it has not been introduced in routine clinical practice because it is too complicated to be performed and is time-consuming (Joosten and Hulst 2013).

The STAMP tool (McCarthy et al. 2008) is a much easier screening tool for use in paediatric care and its use has been validated in hospitalised children aged two to 16. The STAMP consists of five steps (likelihood of the diagnosis to cause undernutrition; child's current nutrient intake; height and weight centile; calculation of the risk score for undernutrition based on the previous steps and the care plan). Children are classified at high medium and low risk of undernutrition. The high risk patients are referred to the dietitian, nutrition support team or consultant; the medium risk patients are monitored and reassessed after three days and the low risk patients

are reassessed weekly. However, similarly to the SGNA, this tool has not been validated for its use in paediatric oncology.

The most recent undernutrition screening tool developed for the general paediatric is the PYMS (Gerasimidis et al. 2010) . This tool is based on the current guidelines for nutritional screening published by the ESPEN (Kondrup et al. 2003). It is a four stage assessment tool based on BMI cut off points; recent weight loss; decreased dietary intake from previous the week; whether the child‘s diet will be affected by admission / condition in the next week.

Gerasimidis et al. (2010) assessed the validity of the PYMS conducted by a nurse by comparing the outcome against a full dietetic assessment as golden standard in 247 children admitted to hospital with several diagnoses. The study also compared the PYMS to the STAMP tool completed by a dietitian. The prevalence of patients identified at risk of undernutrition varied significantly between the screening tool and the full dietetic assessment. For example, the nurse assessments identified fewer high risk patients than the PYMS and STAMP completed by a dietitian, but more that the full dietetic assessment. However, the study showed a high specificity and sensitivity of the PYMS when completed by a dietitian compared to the full dietetic assessment. These findings highlight the issue of misclassifying well nourished patients and how the prevalence of nutritional risk can vary depending on the assessor. The misclassification of nutritional risk would cause an increased workload for the dietetic staff and increased costs for the health service. However, the authors believed that further training and continual use would increase diagnostic accuracy in non dietetic staff which is further supported by a previous study carried out by the same authors (Gerasimidis et al. 2001). The study (Gerasimidis et al. 2001) demonstrated that the PYMS does not produce large numbers of false cases when carried out by trained staff.

To date there is not a study that focused on validating any of the above undernutrition screening tools in the paediatric oncology cohort. At present, the nutritional screening of children with malignancies at the Royal Hospital of Sick Children in Edinburgh is carried out by using PYMS completed by the nursing staff. As previously discussed the PYMS and the STAMP are simple methods based on

weight and height measurements expressed as BMI, nutrient intake and nutritional implications of the disease. However, the use of those tools may be misleading when used to screen paediatric oncology patients for nutritional risks.

The use of weight and height related measurements are thought to be deceptive in paediatric oncology practice. This is because they do not assess body composition and the weight of tumour mass (Smith et al. 1991), oedema, the increased body fat caused by steroid therapy (Ahmed et al. 2002) and the rapid change of fluid in response to chemotherapy, are likely to affect body weight and mask undernourishment. Furthermore, the initiation of nutritional intervention based on the false classification of high risk patients (Gerasimidis et al. 2010), their decreased nutrient intake, or the classification of cancer as a high risk of nutritional implications alone, can lead to unnecessary nutritional intervention. This may lead to an increased risk of developing obesity after recovery plus an unnecessary work load for the dietitian and extra cost for the health service. Therefore, there is evidence to indicate the inappropriate use of the STAMP and PYMS tools in paediatric oncology practice.

To date, there has been only one screening tool devised to look specifically at nutritional risk in this specific population group (Attard-Montalto et al. 1998). This screening tool is based on symptoms that alter nutrient intake and food absorption rather than anthropometrical indices; however it has not yet been validated. Attard-Montalto and co-workers (1998) conducted a prospective study to compare the ability of their Symptom Score (SS) to assess the nutritional status of children treated with chemotherapy in comparison to anthropometric indices (weight, height, BMI, MUAC , TSF, and bioelectrical impedance analysis (BIA) serum albumin, insulin like growth factor-1 (IGF-1) IGF binding protein 3 (IGFBP-3) and whole protein turnover (WBPT). They recorded 511 symptom scores over 24 months in 30 patients (mean and median 17 per patient) aged between 0.7 and 17.5 years. They found no correlation with anthropometric measurements or IGF1 and IGFBP-3 but they reported a correlation of the SS with protein breakdown. From these results they suggested that the SS is better than the other parameters taken into consideration in

the study for assessing nutritional status during therapy. However, this SS has not been validated since its initial description, nor has it been taken up into routine use.

The lack of a specific and widely accepted screening paediatric tool has been reported as the main limiting factor for improving nutritional support in hospitalised patients (Kondrup et al. 2003a; Kondrup et al. 2003b). For this reason it is essential to design a screening tool based on data from this particular patient's cohort and to validate it with respect to clinical outcome. The first stage in the design of such a tool is to identify the risk factors for the development of undernutrition and evaluate the usefulness of commonly used anthropometric measurements in this unique population group. Furthermore, with the robust evidence of the increased risk of obesity for certain type of childhood malignancies and the evidence of a worse outcome for obese patients (Butturini et al. 2007) the nutrition screening tool for this population should also take into account the likelihood of developing over-nutrition as a consequence of childhood malignancy. Patients at high risk of obesity should also be classified as at risk of undernutrition and nutritional management should be as important as for those at risk of under-nutrition.

1.6.2 Nutritional status assessment

Several ways have been suggested as a means of assessing nutritional status for both research and clinical purposes; subjective global assessments (SGA), anthropometry and blood biochemistry are an example (Zunft 1992; Zunft 1992). However, none of these single methods gives an overall picture of nutritional status for all the nutrients. Furthermore, many issues have been identified in the assessment and interpretation of nutritional status in children with cancer.

During cancer treatments actual weight can be affected by hydration status and tumour mass, masking body weight loss (Pietsch and Ford 2000; Smith et al. 1991). Additionally, it has been shown that children treated for cancer experience a change in the distribution of body compartments , with decreased FFM and FM (Murphy et al. 2010). For this reason, many authors argued (Murphy et al. 2009; Murphy et al. 2010; Smith et al. 1991) that the measurement of body compartments (FM and FFM) can provide more valuable information about nutritional status than weight related measurements alone. Additionally, the assessment methods must be accurate and

precise (Atkinson and Nevill 1998; Jamaiyah et al. 2010; Ulijaszek and Kerr 1999). These concepts are discussed in depth later in Chapter three.

The practicality and cost of the measurement in children treated for cancer is also crucial and it can be a limiting factor when assessing their nutritional status. For example, some techniques to assess body composition such as a Dual-energy X-ray absorptiometry (DEXA scan) are very expensive, therefore are not used routinely in this cohort. Finally, the interpretation of the measurements relies on the availability of reference values which should reflect the population characteristics and the study design (Gorstein et al. 1994). However, reference values for the UK population are often available for some methods but not for others, making interpretation of the results problematic.

This section will discuss the use of the methods available in clinical practice and in research and their capability to assess nutritional status along with the issues involved with their use. This list of techniques is not exhaustive but covers the main methods relevant to this current study and to the paediatric oncology clinical environment.

1.6.2.1 Subjective Global Assessment

Currently, at the RHSC Edinburgh, nutrition support is initiated on the basis of a subjective global assessment (SGA) performed by the oncology multidisciplinary team and the hospital nutrition support team. The global assessment is based on weight loss, energy, nutrient and fluid intake, gastrointestinal and other symptoms (Detsky et al. 2008). SGA is considered a simple and inexpensive means of measuring nutritional status. Its use in general paediatric has been reported to be reproducible and precise in assessing hospitalised children (Secker and Jeejeebhoy 2007). However, it needs to be performed by an experienced practitioner, particularly where there are diagnoses in paediatric cancer. Nevertheless its use in paediatric cancer patients has not been validated yet and it has been shown (Cooper et al. 2002), to be largely subjective, inaccurate and not reproducible in adults. Therefore, it is not clear whether this tool is acceptable in paediatric cancer patients.

1.6.2.2 Anthropometric measurements

The word anthropometry comes from the Greek words *anthropos* "man" and *metron* "measure" therefore it literally means measurements of man (Gore et al. 1996). Anthropometrical techniques include height (H) weight (W), body mass index (BMI), TSF and MUAC among others, and they have been used extensively to assess the nutritional status in both research and clinical settings.

The most widely used tool to assess nutritional status in general paediatrics, is the assessment of BMI centile (Cole, Freeman and Preece 1995). BMI does not require any specific expertise, it is cheap and easy to carry out in both clinical and research settings. Furthermore, it is a non-invasive technique, which makes this method easily acceptable by children and their parents. In adults, BMI correlates with FM independently of age and gender, and cut off point are used to identify those underweight (BMI < 18.5), normal weight (BMI 18.5-24.9) overweight (BMI ≥ 25) and obese (BMI ≥ 30) (WHO 2004). However, in children FM is dependent on age and gender. Therefore, the most appropriate way of interpreting BMI is by comparison to national reference data according to age and gender as centile (Cole et al. 1995; Cole et al. 2007).

Triceps Skin Fold (TSF) and Mid Upper Arm Circumference (MUAC) are also measurements easily available and relatively cheap to obtain in both clinical and research setting. However, contrary to BMI, these methods require some level of expertise and training (Gore et al. 1996) and are not generally used in oncology clinical practice. TSF measurement assesses the amount of subcutaneous fat which indicates the energy reserves stored as fat tissue, while MUAC measurement assesses the muscle size which reflects protein reserves stored as lean body mass (Frisancho 1974; Frisancho 1981). These two measurements are single sited and they have been suggested not to be accurate for estimating total body composition in adults because of the uneven distribution of fat. However, they have been reported to reflect body composition in children, where fat deposits are more evenly distributed (Roche et al. 1981). Furthermore, MUAC and TSF are believed to be accurate for measuring changes in nutritional status over time which is the intent of this current study (Kyle et al. 2004b). Accuracy of TSF and MUAC depends on the observer's

skill and training. However, the use of standardised protocols, a single trained observer and suitable equipment has been reported to improve accuracy and reproducibility (Jebb and Elia 1993).

Because a child's body composition depends on age and gender, TSF and MUAC are compared to expected frequencies and are converted to centiles. However, there are no specific TSF and MUAC charts for the UK population , hence the WHO reference value up to a year and the Frisancho for over one year of age (Frisancho 1974; Frisancho 1981) are generally used. This reference data is from the early 70s and is based on US data for white subjects from one year of age. TSF and MUAC can be combined to calculate fat mass area and muscle mass area using published equation (Frisancho 1974) to assess FFM and FM body stores. Arm muscle mass and fat muscle mass have been reported to overcome the underestimation of tissue changes in the upper arm observed in TSF and MUAC alone (Frisancho 1981). However, the equation does not take into account the subject variation of bone diameter when measured by MUAC (Frisancho 1981).

It has been widely reported that the level of undernutrition among childhood cancer patients varies with the method (Murphy et al. 2009; Sala et al. 2004) and the definition of undernutrition utilized (Pietsch and Ford 2000). Although height and weight related measurements are easy and cheap to measure (Mei et al. 2002) (Murphy et al. 2009), their use is believed to be misleading in paediatric oncology practice. The reasons for this, are that body weight related measurements do not assess body composition and the weight of tumour mass (Smith et al. 1991), oedema and increased body fat caused by steroid therapy (Ahmed et al. 2002) can affect body weight and mask undernourishment. Therefore, many authors (Garofolo et al. 2005; Oguz et al. 1999; Smith et al. 1991) have suggested TSF and MUAC as better nutritional assessment methods in this particular cohort.

Several studies have aimed to evaluate the best anthropometric methods to assess nutritional status in children treated for cancer (Murphy et al. 2009; Nething et al. 2007; Oguz et al. 1999; Pietsch and Ford 2000; Smith et al. 1991; Smith et al. 1991). There is strong evidence to support the use of arm anthropometry as a better assessment method of undernutrition in children treated for cancer (Garofolo et al.

2005; Oguz et al. 1999; Smith et al. 1991). A large prospective controlled study (Smith et al. 1991) showed that, even though W/H were normal, arm anthropometry was significantly lower in a cohort of 100 newly diagnosed British children with cancer when compared to control and reference values. Remarkably, the difference between W/H and arm anthropometric measurements on assessing undernutrition was not observed the control group, further supporting the idea that the tumour and cancer treatment may have a masking effect on undernutrition when measured by weight related measurements.

Further work to support TSF and MUAC as better indicators of undernutrition comes from a later study (Oguz et al. 1999) which detected a much higher incidence of undernutrition (27%) than reported by Smith and co-workers (1991). The reasons for the difference in undernutrition incidence between the two studies are not clear. Possible explanations are the differences in the cancer type included in the study. The first study (Smith et al. 1991) included both haematological and solid cancers, whereas the Oguz et al. (1999) included only solid cancers. Furthermore the racial and socioeconomic differences between the two groups of patients may also account for this difference since the Smith et al. (1991) was carried out in British patients and the Oguz et al. (1999) study was carried out in Turkey.

Further supporting evidence has been reported by a cross sectional study (Garofolo et al. 2005) conducted in 127 Brazilian patients during the first phase of treatments. A significantly higher percentage of undernutrition was detected by using TSF (40.2%) and MUAC (35.4%) compared to W/H (18.9%). Compared to the Smith et al. (1991) study the reported incidence of undernutrition was much higher which is likely to be a reflection of the socioeconomic status of the country where the study was carried out.

Two later studies (Nething et al. 2007; Pietsch and Ford 2000) aimed to compare the use of weight and height related measurements (BMI, weight for height (W/H), weight for age (W/A) and height for age (H/A). Pietsch and Ford (Pietsch and Ford 2000) conducted a retrospective study on 127 American children with several types of cancers and they observed a variety in the rate of undernutrition at diagnosis in the same cohort ranging between 1% to 46%, depending on the method used for the

nutritional status assessment. They concluded that BMI <-1SD was the better assessing method since it detected the highest undernutrition rate compared to the weight and height related measurements (BMI, weight for height (W/H). However, this study used a very loose cut off point (BMI <-1SD) to define undernutrition instead of the BMI ≤-2SD (World Health Organisation 2011) generally used to define undernutrition. Hence, it is very possible that it resulted in an unverified high prevalence of undernutrition, therefore BMI <-1 SD should not be used. Furthermore, this study did not use arm anthropometry, so it is not possible to draw any conclusion regarding the comparison of height and weight related measurements and arm anthropometry.

Conversely, Nething et al. (2007) failed to show the usefulness of BMI as an indicator of undernutrition in children with malignancies and they reported a lack of agreement between BMI centile and H/A and W/A. Furthermore they reported that BMI for age classified too many patients as being at risk of under-nutrition compared to the other measurements. However, those measurements were not compared against a gold standard and it is not possible to conclude whether BMI causes an overestimation of undernutrition or whether H/A and W/A caused an underestimation.

The evidence strongly suggests that weight related measurements as the only measurements of nutritional status in childhood cancer may be not reliable enough. However, it may be argued that the higher incidence of undernutrition measured by arm anthropometry is not caused by a better measurement but by misclassification and the generation of false positives which lead to higher rates of undernutrition. However, this is very unlikely because it has been shown that TSF correlates with FM% obtained from air displacement plethysmography in children undergoing cancer therapy (White et al. 2011), which is a reliable and valid technique to assess body composition in children (Fields et al. 2002). Importantly regardless of the reliability of each method, these findings imply that many undernourished patients are not identified and patients with solid tumour are most likely to be missed by weight related measurements. Given the pivotal role of assessing nutritional status in this cohort, and the fact that most common clinical practices rely on weight related

measure to assess nutritional status, the lack of an appropriate nutritional assessment method negatively affects the nutritional management of children treated for cancer.

1.6.2.3 Bioelectrical Impedance

Bioelectrical impedance (BIA) has been extensively used to assess the nutritional status of healthy adult subjects. This technique does not require any specific expertise, it is quick to be performed and it is relatively non invasive. BIA assesses body composition by measuring resistance and reactance at a specified electrical frequency. The tissue conductivity is determined by the concentration of fluid and electrolytes present. Therefore, from those measurements, using a validated prediction equation, it is possible to obtain total body water (TBW) which is an indication of lean body mass (LBM) and FM (Zunft 1992).

The use of BIA in healthy adults (Berger et al. 2000; Haas et al. 2012) has been shown to be accurate for estimating body composition. However, the use of BIA for nutritional assessment in paediatrics is controversial. A satisfactory level of accuracy for estimating FM has been reported by some authors (Okasora et al. 1999; Schaefer et al. 1994; Wabitsch et al. 1996) but not by others (Hosking et al. 2006). Many factors could contribute to the disparity found in the literature, with the main one being the lack of a specific paediatric prediction equation (Schaefer et al. 1994).The equations available for healthy adults are not applicable in children due to the fact that children experience changes in the proportion of fluid compartments during growth and development, therefore a specific equation specifically designed for children must be used in relation to age (Boileau et al.1984; Deurenberg et al. 1990; Houtkooper et al.1989). However, the validation studies needed to design the prediction equation in children are challenging for many reasons. For example, the estimation of FFM from total body water techniques is based on the assumption that FFM is constant, which, as discussed, is not the case in children (Boileau et al. 1984; Deurenberg et al. 1990; Houtkooper et al. 1989). Furthermore techniques such as densitometric underwater weighting, requires a high level of subject cooperation which is unlikely to occur in young children. Although there are some equations available for paediatrics (Clasey et al. 2011; Schaefer et al. 1994) there is not a validated equation available in the literature for the use in children with cancer.

Another factor that can impact on the impedance results is the type of analyser used. There are two main methods for bioelectrical analysis, the single frequency BIA (SF-BIA), generally at 50 KHz and the multi frequency BIA (MF-BIA) using different frequencies ranging from 0 to 500 KHz. The SF-BIA measures a sum of extra cellular water (ECW) and intra cellular water (ICW) therefore it can estimate total body water without distinguishing between the two compartments. In contrast, multi frequency BIA (MF-BIA) can evaluate TBW and ICW and ECW distinctly (Kyle et al. 2004). For this reason the SF-BIA has been indicated to be more accurate than the MF-BIA when assessing patients with normal hydration (Gudivaka et al. 1999)) whereas the MF-BIA has been reported to be more accurate when measuring subjects with altered hydration (Patel et al. 1996).

The value of using the BIA technique in clinical, where the disease and the treatments may have cause a fluid shift, is still under debate (Kyle et al. 2004a). Few studies (Fredrix et al. 1990; Simons et al. 1995) have shown a correlation between BIA and the reference method (deuterium dilution technique) to predict total body water in adult cancer patients. The Simons and co-workers study (Simons et al. 1995) used a single frequency 50Hz BIA among a heterogeneous group of adult cancer patients with and without cachexia. FFM was calculated using a prediction equation developed from normal weight healthy adults (Lukaski and Bolonchuk 1988) and it was compared to the deuterium results. In the 41 patient studies, the TBW was found to be overestimated by 5% (1.67 l) in underweight patients (n=16), whereas it was found to be strongly correlated with the deuterium technique (r^2= 0.85) in normal weight patients (n=25). The reason for this inconsistency between the normal weight and underweight group is probably due to the shift in fluids caused by cachexia, which may have altered the conductivity of body compartments. Therefore, BIA may not be able to assess body composition in patients with significant shifts in fluid especially if used with a prediction equation developed for a healthy group.

Since paediatric cancer patients are likely to have altered hydration status caused by the treatments and the disease (Warner et al. 2004) the regression equation developed for healthy children (Clasey et al. 2011; Schaefer et al. 1994) is likely to

result in substantial error and should not be used in paediatric cancer patients. The only available equation for the paediatric cancer cohort is the Brennan and co-workers (Brennan and Thomas 1997). The equation was validated against the deuterium-oxide technique on a study carried out on 40 children newly diagnosed with solid and haematological tumours. However, it is not clear from the article published whether they use a SF-BIA or a MF-BIA. The study showed a wide limit of agreement (mean 0.9, limit of agreement = -2.46 to 4.06) between deuterium technique and BIA. This shows some level of inaccuracy and it suggests that more work is needed to increase the BIA precision in assessing this group of patients. Only one study used the BIA technique to assess nutritional status in paediatric cancer patients and it was published in the same year as the Brennan equation (Dubuque et al. 1997). Therefore, the study used an equation (Schaefer et al. 1994) for general paediatrics to calculate FFM. However, even though the equation was not specific for children with cancer they reported no difference between the FFM obtained from TSF and the BIA. The level of accuracy is likely to have been increased by the use of a MF-BIA which may be due to it being a better device to measure subjects with altered hydration status (Patel et al. 1996). However, these results must be interpreted with some caution since the authors did not compare the FFM % against a gold standard using arm anthropometry instead.

Another issue in the use of BIA for the assessment of undernutrition in children with cancer is the limited availability of FM reference data for children from birth to adulthood. To date there are only three studies that provide FM reference values for paediatrics (Fomon et al. 1982; Laurson et al. 2011; Wells et al. 2012), however they cover different age groups and were carried out using different validation methods. Only one study (Fomon et al. 1982) provides reference values from birth, but it has the big limitation of using only one subject. The reference data in this study were determined using the deuterium technique and the data is presented as FM%. The Laurson et al. study (2011) provides references expressed as FM % as the Fomon et al. study (1982) and it covers the age range from five to eighteen years and the reference data was obtained using skinfold thickness measurements coming from the National Health and Nutrition Examination Survey (NHANES) IV based on 8289

subjects. Although this study had the advantage of a big sample size, the FM% was not obtained using a gold standard.

Very recently, reference data for UK children aged five to twenty have been published as FM and FFM SDS and centiles (Wells et al. 2012). The study assessed body composition by using the air displacement plethysmograpy, in a sample of 535 British children. Although the study has the great advantage of a big sample size and a good study design, it has the limitation of covering only children from five years of age.

Therefore, the lack of comprehensive reference data from zero years of age onwards, is a further limiting factor on the assessment of body composition in children. However, whilst comparison of FM against reference values may be limited by this lack of reference values, it provides a useful measurement to examine changes in body composition in response to cancer and its treatments in longitudinal studies.

1.6.2.4 Energy and nutrient intake assessment methods

A variety of methods may be employed to estimate energy and nutrient intake with the preferred method of choice in the childhood cancer literature being the dietary recall (Delbecque-Boussard et al. 1997; Poslusna et al. 2009; Sgarbieri et al. 1999) and the dietary diary (Bond et al. 1992; Carter et al. 1983b). These assessment methods are self reported and each method is subject to some extent of error (Biro et al. 2002). Weighted diet diaries overcome the issue of estimating portion sizes and minimize the error resulting from memory lapses (World Health Organisation 1995). However, although it has been shown to provide a relative reproducible estimate of energy intake and macronutrients (Willett 1998; Willett 1998) , this method has a big respondent burden since it requires that all food eaten must be methodically weighted and recorded (Pekkarinen 1970). This methodology therefore is very demanding for the families and the patients undergoing cancer treatments. Similarly, the dietary records using portion sizes instead of the weight still require participant involvement and the participant must be very motivated. Moreover, if a meal is not recorded as it is eaten, the errors increase (Biro et al. 2002). In contrast, the dietary recall method has the great advantage of having a small respondent burden and hence it is suitable for a dietary assessment during cancer treatments. Other

advantages are that there is no requirement for literacy and this procedure does not alter the pattern of food intake because it is done retrospectively. However, this approach depends on the respondent's recall and estimation of portion sizes and only provides information on a single day intake but also has an increased error due to recall.

Validation studies in children have shown that both weighted dietary diary and diet history tend to underestimate energy intake in children and adolescents (Bandini et al. 1990; Bratteby et al. 1998) and are affected by under-reporting (Black et al. 1991). Moreover, multiple pass 24 h recall has been reported to be accurate on a group level but not at an individual level (Johnson et al. 1996). Therefore, there is not a perfect method to assess dietary intake and the choice of one method over another should consider feasibility and the nutrient to be measured and the interpretation of the results should take into consideration the limitations of the method used.

1.6.2.5 Blood biomarkers

Selected blood biomarkers such as albumin, pre albumin, transferrin and retinol binding protein have been extensively used (Forse and Shizgal 1980; Kirby 1997; Santos et al. 2003) to assess nutritional status with serum albumin being the most frequently used among all the blood parameters. However, the ability of blood proteins to assess nutritional status has been subject to much debate (Forse and Shizgal 1980; Kirby 1997; Santos et al. 2003). The rationale behind the use of albumin as a biomarker of nutritional status is that, during chronic protein undernutrition, when the main energy source is carbohydrate, the secretion of insulin prevents muscle breakdown to replace albumin thus leading to hypoalbuminemia. However too many non nutrition markers contribute to a low plasma concentration (Lipman 2005). Among all, albumin is an acute phase reactant and hypoalbuminemia is caused by inflammation as sparing mechanisms to sustain the synthesis of inflammatory chemicals needed to maintain the inflammatory response (Bistrian 1986).

Many studies (Donaldson et al. 1981; Forse and Shizgal 1980; Merritt et al. 1985; Santos et al. 2003) have shown a poor specificity and sensitivity of albumin in

measuring nutritional status with hypoalbuminemia being caused by inflammation and fluid shifts rather than protein undernutrition in hospitalised patients (Forse and Shizgal 1980; Santos et al. 2003) and paediatric oncology patients (Donaldson et al. 1981; Merritt et al. 1985). Furthermore, it is well established that plasma albumin recovers when the clinical condition improves (Charney 1995), but not in response to artificial feeding (Ireton-Jones and Hasse 1992) which highlights albumin as a disease marker more than a nutritional status indicator.

Retinol binding protein (RBP) and transferrin are also used in the clinical setting to assess protein undernutrition. Retinol binding protein is the protein carrier for retinol and its serum concentration is believed to reflect retinol serum levels and therefore undernutrition (World Health Organization 1996). Serum transferrin is the transport protein for iron. However, similarly to albumin, a decreased concentration of serum transferrin (Ruggiero and Riccardi 2002) or RBP level (Gamble et al. 2001) could be caused by inflammation and infection and be mistaken for undernutrition. Furthermore, the use of this parameter in cancer patients may not be appropriate since cancer is associated with anaemia. Serum iron is often decreased (Tessmer, Hrgovcic, and Wilbur 1973) but levels of ferritin are extremely elevated and transferrin saturated. Therefore, albumin RBP and transferrin are believed not to be a good measurement of undernutrition in this cohort (Gamble et al. 2001; Merritt et al. 1985; Ruggiero and Riccardi 2002).

The role of albumin as an indicator of inflammation more than nutritional status has been addressed by Merritt and co-workers (Merritt et al. 1985). The study was specifically designed to determine the implication of hypoalbuminemia in 90 children treated for a combination of malignancies. They observed abnormal serum albumin associated with normal anthropometrical nutrition parameters. Furthermore, an association of hypoalbuminemia with fever was reported. Therefore, this study further supports the role of hypoalbuminemia as an indicator of acute metabolic response to infection more that undernutrition in paediatric cancer patients.

Contrasting evidence comes from other studies (Kibirige et al. 1987; Yu et al. 1994). Kibirige and co-workers (1987) reported serum albumin concentration of less than 32g/l as a useful indicator of poor nutritional status measured as weight loss greater

than 5% in newly diagnosed children with ALL. However this study did not measure markers of inflammation and it is not possible to establish if the decreased serum albumin was caused by inflammation or by undernutrition. Moreover, Yu et al. (Yu et al. 1994) investigated the use of the biomarkers previously described, Pre Albumin (PA) RBP and transferrin as sensitive indicators of mild and moderate undernutrition in 25 leukemic children, either in remission or newly diagnosed. The authors used pre-albumin as a better indicator of undernutrition in paediatrics compared to albumin because it has higher turnover rate compared to albumin (half -life 1.9 days, 20 days respectively); therefore a limited substrate supply would cause a much quicker drop in plasma concentration of pre-albumin than albumin. In order to exclude low levels of blood biomarkers caused by inflammation they measured CRP levels. CRP levels were comparable to the healthy children 50% of patients were found with lower blood PA concentration than the expected rank for their age and gender, whereas only 10-18% has lower blood concentration of albumin, transferrin and retinol binding proteins. Therefore, they concluded that PA was a good indicator nutritional status when compared to the other blood parameters. However, steroids are known to decrease CRP levels (Felson et al. 1995; Mitchell 2006) and the patients in the two studies (Kibirige et al. 1987; Yu et al. 1994) were ALL patients treated with high doses of steroids as part of their cancer treatments. Furthermore hepatic synthesis of albumin has been shown to be increased by steroids (Oppenheimer and Werner 1966). Therefore, the treatments are likely to have impacted on the inflammation markers and on the synthesis of albumin, causing the debatable results.

This literature review highlights the lack of a convenient, sensitive, specific and measurable indicator of undernutrition in paediatric oncology. Comparisons between the results available in the literature to determine the best tool to assess nutritional status in this specific cohort are difficult because of the difference in sample size, type of cancer and assessment methods used. Furthermore, the evidence puts into question the accuracy of the current simple nutritional measurements, based on weight and height related measurements, in paediatric oncology. Based on this evidence, it is very likely that some undernourished children with cancer assessed for undernutrition based on weight and high are missed and that body FM stores should

also be assessed. It is true that children experiencing evident nutritional problems during cancer therapy are globally assessed; however the problem is in identifying those who do now show any obvious sign of undernutrition and those at risk. Therefore it is now essential to address this issue and it is necessary to evaluate nutritional risks on a global scale in conjunction with all the factors believed to play a role in the development of undernutrition in this specific population.

1.6.3 Micronutrients status

So far, this review explored the malnutrition in paediatric oncology patients as a consequence of energy imbalance. However, cancer and its treatments can also result in a selective impairment of intake, reduced absorption and net losses of micronutrients with a detrimental effect on micronutrients status (Foltz et al. 1996; Grant and Kravits 2000; Greene et al. 1994; Van Cutsem and Arends 2005). Furthermore, paediatric cancer patients may have an increased metabolic demand for micronutrients, for example as a consequence of increased REE and the consequent increased demand for co- factors and enzymes. However, the specific micronutrient requirements for this cohort are unknown and micronutrient assessment in this group can be challenging. Micronutrient assessment in a clinical setting is generally carried out using plasma samples; however, many factors affect plasma micronutrient concentration such as post prandial status, exercise and, of particular relevance to this cohort, inflammation (Tomkins 2003). Furthermore, plasma levels of some nutrients (e.g. copper), may not reflect tissue concentration and nutrient status Therefore, the altered plasma levels of some nutrients (e.g. zinc, ferritin, copper) may be caused by the use of an inappropriate assessment technique (Aggett and Davies 1983) or by inflammation (Galloway et al. 2000; Tomkins 2003) rather than undernutrition per se. Thus, this possible interaction must be taken into account when interpreting the results.

Although many studies have aimed to assess plasma vitamins and trace element concentration in adults (Durken et al. 1995; Nakagawa 2000), only few studies have been carried out in children to assess the nutritional status of vitamin and trace elements during childhood cancer therapy. However, all the evidence showed a detrimental effect of cancer and its treatments on micronutrient status.

1.6.3.1 Vitamin A, C , E.

Vitamin A, C, and E are dietary factors with antioxidant properties and they have protective effects during cancer. For example, vitamin A and E induce cell differentiation and growth inhibition in vitro in some types of cancer cell (Prasad and Edwards-Prasad 1982; Prasad and kumar 1996; Sporn and Roberts 1983) and In vivo studies have shown a decrease in tumour size in response to high doses supplementation with vitamin A (Gundimeda et al. 1993; Prasad et al. 1993). Similarly, vitamin C has been shown to inhibit cancer growth in cells cancer culture in a dose dependent manner (Prasad 1980). However, some other authors observed an increase in cancer growth at small doses and different types of cancer (Prasad et al. 1994), which may suggest different effects of vitamin C in cancer depending on the dose and the type of tumour. Furthermore, these nutrients are essential to maintain growth and development, therefore, their adequate status in children during cancer therapy is pivotal.

Alterations in plasma concentration of vitamin A, C and E have been described in children undergoing treatment for cancer. A study (Fiore et al. 1997) reported a significantly lower level of plasma vitamin A in 54 children with cancer at onset of the disease in comparison to a matched healthy control. Since only 33% of the cohort had an inadequate dietary intake of the vitamin, this study would suggest an increased requirement for the vitamin; however, vitamin A intake was assessed by 48 h dietary recall which is not a very accurate means of assessing micronutrient intake (Poslusna et al. 2009). Unfortunately the study did not measure plasma vitamin A after therapy had started therefore, effects of treatments on plasma vitamin A is unknown.

Further work to support the increased risk of vitamin deficiency during childhood cancer come from Malvy et al. (1997). They observed a low plasma retinol, β-carotene, and α-tocopherol in 170 children with several types of cancers at diagnosis compared to 632 healthy matched controls. The study did not assess nutrient intake, therefore it is not clear what were the causes for the reduced plasma level at baseline and whether the improvement observed at six months was caused by nutrient intake or by other factors.

Data from other studies (Kakar et al. 1975; Neyestani et al. 2007) also suggests a poor vitamin C status in this cohort. A study (Kakar et al. 1975) showed a lower plasma and leucocytes vitamin C concentration in ten ALL patients compared to control even though vitamin C dietary intake was similar. These finding would suggests an increased need for vitamin C in patients treated for ALL. However, from this study it is not possible to determine the causes for the increased requirement.

The effect of micronutrients with antioxidant properties supplementation during cancer therapy is still unclear. Some oncologists may argue that the supplementation of antioxidants may interact with cancer treatments by protecting both healthy cells and tumour cells against oxidative species generated by those treatments to destroy the tumour. However, some studies have shown that vitamin C, A and E enhanced the growth inhibitory effects of many chemotherapeutic agents (Prasad et al. 1979; Prasad 1980; Prasad et al. 1999; Ripoll et al. 1986). Moreover, those vitamins play an essential role in many other body functions and their nutritional status must be adequate to sustain growth and development during childhood cancer. Hence, the role of supplementation needs to be elucidated further especially to understand the specific requirements for those nutrients during cancer therapy.

1.6.3.2 Vitamin D

Vitamin D is currently attracting a great deal of scientific and media attention in the UK. Due to the lack of sunlight exposure and with very few foods being fortified with vitamin D ,children and adults are at high risk of being deficient or insufficient (Holick 2006a; Holick 2006b). Vitamin D deficiency can cause secondary hypoparathyroidism. A decreased secretion of the parathyroid hormone (PTH) is a secondary response to calcium and vitamin D deficiency. PTH enhances calcium release from the bone and the conversion of the inactive form of vitamin D to its active form Vitamin D (1,25-dihydroxy vitamin D). Therefore vitamin D deficiency can cause bone mass loss (Sahota et al. 1999; Sahota et al. 2001) with detrimental effects in bone growth and development, particularly important in children (Baradaran et al. 2012; Goshayeshi et al. 2012; Zwart et al. 2011).

Vitamin D status has been reported to negatively correlate with BMI in adults and adolescents. Hence obesity may be a risk factor of vitamin D deficiency per se, and

if the secular trend towards an increased prevalence of obesity is considered, it is likely that the prevalence of vitamin D deficiency will also increase even at adequate sunlight exposure (Baradaran et al. 2012; Goshayeshi et al. 2012; Zwart et al. 2011). The role of Vitamin D goes beyond growth and development. Recent studies have also shown that vitamin D is protective against cancer (Holick 2006b; Mantell et al. 2000) by inducing apoptosis and preventing angiogenesis. Therefore, this evidence highlights even further the importance of vitamin D during childhood cancer therapy.

Children treated for cancer have an increased risk of poor vitamin D status since they may not rely on the vitamin D_3 synthesis on the skin, for the limited time spent outdoors or dietary intake to meet their vitamin D requirements. Furthermore, patients treated for leukaemia may have a higher risk of deficiency (Skversky et al. 2011) due to the increased vitamin D catabolism caused the steroids (Zhou et al. 2006) and for the effect of steroids therapy on increasing FM and BMI (Reilly et al. 2001; Reilly 2009; Ventham and Reilly 1999).

Plasma vitamin D has been reported to be insufficient in the paediatric oncology population at all stages of treatment (Helou et al. 2008; Sinha et al. 2010; Halton et al. 1996). Halton and co-workers (Halton et al. 1996) observed vitamin D plasma levels below normal range in 70% of children (n=40) treated for ALL at both diagnosis, and after one year of treatments. Lower prevalence of plasma vitamin D deficiency has been reported elsewhere (van der Sluis et al. 2002), where only 20% and 4.5% of ALL patients (n=61) had decreased plasma vitamin D at diagnosis and during therapy respectively. This inconsistency may be explained by the different cohort characteristics. The Holton et al.(1996) study contained a higher percentage of high risk patients compared to the van der Sluis et al. (2002) study, which are treated with higher doses of corticosteroids compared to the low risk patients.

Vitamin D supplementation has been reported to improve vitamin D status in all patients apart from the haematological group (Helou et al. 2008). This difference response to vitamin D supplementation observed among the diagnostic groups may be explained by the increased vitamin D catabolism in ALL patients consequent to steroid therapy (Skversky et al. 2011) or by the increase in BMI caused by steroids. However, vitamin D status was not correlated to BMI to investigate any independent

risk of obesity in vitamin D status (Baradaran et al. 2012; Goshayeshi et al. 2012; Zwart et al. 2011) in any of these studies (Helou et al. 2008; Sinha et al. 2010).

1.6.3.3 Zinc copper and selenium

Several studies have described zinc deficiency in paediatric cancer patients (Carpentieri et al. 1986; Cavdar et al. 1980; Gupta et al. 1994; Malvy et al. 1997; Mocchegiani et al. 1994; Sgarbieri et al. 1999) and it has often been reported with increased plasma copper (Delves et al. 1973; Gupta et al. 1994; Sgarbieri et al. 1999; Tessmer et al. 1973). However, zinc and copper are acute phase reactants and the changes in plasma concentration described in these studies may be caused by inflammation rather than undernutrition (Galloway et al. 2000). Nevertheless, none of the above studies assessed inflammation and therefore, it is not known if the changes in plasma concentration observed in those studies were cause by inflammation alone or if there was some other mechanism involved. However, the normalisation effect of chemotherapy on plasma zinc and copper may support the role of inflammation as the possible leading cause of imbalance.

Possible other factors playing a role on the observed decreased plasma zinc in cancer are the increased urinary excretion caused by steroids (Flynn et al. 1971) which are often used in anti-cancer therapy, the depressing effect of copper in zinc and their competition for absorption in the intestinal mucosa (Cavdar et al. 1980). Furthermore, zinc deficiency decreases thymulin activity and IL2 production (Prasad et al. 1988) which are essential in T cell and Natural Killer regulation as well has being essential for anti-viral and anti-tumour body response. Interestingly a study (Malvy et al. 1997) reported a reduced level of active thymulin compared to the control group and an extremely high level of its inactive form in children with cancer. When zinc was added in vitro to match the concentration of the healthy control group, the thymulin conversion from its inactive form restarted. The authors suggested zinc deficiency as cause of reduced thymulin. However, it may be possible that decreases plasma level of zinc observed in cancer patients is a consequence of an increased activity of this pathway in response to inflammation, rather than the cause.

Additionally, the decreased concentration of serum zinc may be caused by decreased nutrient intake and absorption. However, of all the above studies only one (Sgarbieri et al. 1999) measured zinc intake by the 24 h diet recall method and found an intake lower than the RDA. Even so, the 24 h diet recall is not an accurate method of measuring trace element intake and their estimate may not reflect the actual intake (Poslusna et al. 2009) and the low zinc intake could have been attributed to the underestimation of the method to measure it, rather than the intake itself. Therefore the hypothesis of low plasma zinc being caused by poor intake has not yet been tested.

Even though inflammation may explain the changes in zinc and copper plasma concentration during the acute phase response it is not clear if cancer and its treatment can further impact the nutritional status of those trace elements. Moreover, the literature lacks intervention studies aiming to explore the effect of zinc supplementation in this cohort. Since the aetiology of this deficiency is still not clear, further research is essential to understand if reduced nutrient intake, reduced absorption and metabolic abnormalities can have an impact on the factors and whether supplementation may reverse this deficiency.

Further work on the trace element status in paediatric oncology patients showed a detrimental effect of cancer and its treatment on selenium status (Pazirandeh et al. 1999; Zuo et al. 2006). A study (Pazirandeh et al. 1999) in newly diagnosed leukaemia patients and a healthy matched control showed normal level of selenium before treatment followed by a drop in serum selenium in the ALL group but not on the AML group after induction chemotherapy. Therefore, the study showed a different effect among the induction treatments for ALL and AML on selenium status. However, it is not clear what the exact mechanisms for the negative effect of ALL treatments are. Contrarily, Malvy and co-workers (1997) did not find any significant difference in newly diagnosed paediatric oncology patients including ALL with a variety of cancer types both at diagnosis and after six months. The contradictory findings are difficult to reconcile, but it may be that, since the ALL patients were not stratified according to risk levels, they may have been in different chemotherapy protocols which may have caused the different plasma concentration.

This literature review of studies highlights the detrimental effect of cancer treatments on vitamin and trace element status in children treated for cancer. However, the specific mechanisms for these changes are still unknown and it is not clear whether they are caused by the inflammatory response of the host to the cancer or by other factors such as increased metabolism, reduced intake and absorption or a combination of those. Furthermore, the specific requirements for this cohort have not been established yet and the consequences of those micronutrient imbalances are unknown. Considering the pivotal role of those nutrients in development and growth, not to mention their potential protective role during cancer treatment, it is now fundamental to clarify this topic.

1.7 Nutrition support in paediatric cancer therapy

When a patient is found to be undernourished by the nutritional status assessment, nutritional therapy may be initiated. However, there are no universally agreed criteria for the nutrition support (NS) duration, timing and type composition of feeds in paediatric oncology probably because of the broad spectrum of the disease and the complexity of the treatments and their side effects (Bauer et al. 2011).

Nutrition support should aim to maintain body stores, support body development and growth. In order to achieve these aims, NS should meet the patient's energy requirements. However, in this population group meeting the energy requirements via NS is extremely challenging. The first limiting factor is the lack of energy reference values specific for paediatric cancer patients which have been discussed previously in this document (Section 1.4.3). Secondly, cancer treatments affect tolerance to feeds, making NS very challenging. The current practice at the RHSC is to calculate energy requirements based on the Oxford equation (Henry 2005) matched for age and gender. However, because of the reduced tolerance to feeds, NS aims to achieve the amount tolerated more the estimated energy requirements.

Nutrition support to treat undernutrition comprises; additional oral calorie supplementation by oral supplements (OS), enteral nutrition (EN) by , introduction of nasogastric feeding, with either boluses or overnight feeding or both, insertion of a percutaneous endoscopic gastrostomy (PEG) with a combination of bolus and overnight feeding or finally total parenteral nutrition (TPN).

Many adult studies have reported that nutrition support during cancer treatments increases outcome and treatment tolerance (Bozzetti et al. 2000; Dresler, Jeevanandam, and Brennan 1987; Odelli et al. 2005). However, some other studies have observed significant TPN complication with no effects on improving nutritional status (Popp et al. 1981) or no significant advantage on improving survival (Freeman et al. 1982). Most of the studies aiming to assess the effectiveness of nutrition support in paediatric cancer patients were carried out with regard to TPN (Donaldson et al. 1982; Ghavimi et al. 1982), with little attention to the use of enteral nutrition in this cohort (Rickard et al. 1979; Rickard et al. 1985). Furthermore, randomized control cohorts have not been employed in many of those studies.

Most of the studies aiming to assess the effectiveness of TPN support in paediatric cancer patients have shown a positive effect on reversing, or preventing protein undernutrition during the initial phase of cancer treatments (Donaldson et al. 1982; Ghavimi et al. 1982; Rickard et al. 1979; Rickard et al. 1985). A prospective randomised trial (Donaldson et al. 1982) (n=39) showed a significant improvement in weight in the TPN group in comparison to the control group. 64% of the TPN group maintained or improved body weight whereas only 17% of the control group did so. However, at three months follow up, the TPN group had a decline in weight and the differences between the two groups were no longer observed. Similar results were also reported by another prospective randomised trial (Ghavimi et al. 1982).

Only a few studies (Smith et al. 1992; den Broeder et al. 2000; den Broeder et al. 1998) have been carried out to look at the efficacy of enteral nutrition to counteract undernutrition in this cohort. A randomised controlled study (Smith et al. 1992) carried out in ten newly diagnosed children with several types of malignancies showed an increased energy intake and an improvement in nutritional status as measured by MUAC in response to nasogastric feeding. Similar results were observed in other studies (den Broeder et al. 1998; den Broeder et al. 2000)

When the efficacy of TPN and EN has been assessed and compared with regard to improving or maintaining nutritional status, it emerged that TPN had a positive effect on all the above aspects in the first few weeks of treatments, whereas EN was unable to achieve any improvement. Rickard et al. (1985) in a randomised control

study showed that TPN improved nutritional status and that EN was not as effective as parenteral nutrition in preventing undernutrition in 32 children newly diagnosed with Neuroblastoma. Similar results were reported in another two studies (Rickard et al. 1989; Rickard et al. 1979).

The contrasting evidence of the ability of TPN and EN to counteract undernutrition reported from the previous studies (den Broeder et al. 1998; Donaldson et al. 1982; Ghavimi et al. 1982; Rickard et al. 1979; Rickard et al. 1983; Rickard et al. 1985; Rickard et al. 1989; Smith et al. 1992) , may be explained by small patient numbers, differences in cancer diagnosis studied, and methodological limitations such as only a few studies being randomised (den Broeder et al. 1998; Rickard et al. 1989; Smith et al. 1992). Furthermore, pharmacologic progress of the anti emetic drugs and their improved ability to counteract nausea and vomiting as a consequence of chemotherapy may have increased the tolerance and efficacy of EN.

The studies where EN was found to be ineffective in counteracting protein energy undernutrition during the intensive phase of treatments (Rickard et al. 1979; Rickard et al. 1989; Rickard et al. 1985) are dated compared to those that showed a positive effect of EN during intense chemotherapy (den Broeder et al. 2000; den Broeder et al. 1998; Smith et al. 1992). Therefore, better management of nausea and vomiting is likely to have increased the tolerance to EN and therefore improved its efficacy in counteracting undernutrition.

Altogether, this evidence stresses the importance of more research aiming to improve nutritional screening and assessment in this cohort. However, considering the increased cancer related obesity risk and the negative effect obesity has in cancer treatment, there is now a need for the consideration of overnutrition as well as undernutrition in this cohort in the nutritional management of paediatric cancer patients.

1.8 The nutritional risks of children with cancer

The previous sections extensively described the increased risk of malnutrition in this cohort and the imminent need for a specifically designed nutritional screening tool. The first step is therefore to identify the risk factors for undernutrition during

paediatric cancer and its treatments. However, the literature is lacking in studies specifically designed to assess the overall risk of malnutrition in paediatric cancer such as age at diagnosis, gender, type of tumour, stage of tumour, treatment modalities and protocols and stage of treatments in children treated for cancer.

The main limiting factors for this type of epidemiological study are the size of the sample required to have enough statistical power to allow data analysis. Therefore, this type of research requires a multicentre approach, which it is very costly to conduct. Furthermore, the attainment of the required sample size in paediatric cancer is even more challenging, since the incidence of paediatric cancer is much lower than adults.

An important multicentre study (Pressoir et al. 2010) was carried out to identify the risk factors for undernutrition in adult cancer patients. The study was conducted in 17 centres and included 1545 patients. Nutritional status was assessed based on BMI and the risk factors analysed were, age, gender, tumour site, treatment type, disease stage, and antibiotic therapy. The univariate analysis showed that in male subjects, specific type of cancer (neck and head, GI) the presence of metastases, hospitalisation, palliative care and radiotherapy were associated with poor nutritional status. Remarkably they did not report any association with chemotherapy or surgery alone. This study had the great advantage of a sample size that allowed statistical analysis. However, the measurements were taken at baseline and after two months and even though they identified several risk factors, they did not assess nutritional risk depending on the phase of the treatment. Furthermore, because of the difference in cancer and its treatments, it is not possible to assume that those findings would be applicable in the paediatric population.

Little is known about the risk factors for undernutrition during treatments in paediatric oncology patients. However, it would appear that the increased risk for undernutrition is associated with a specific type of cancer (solid cancer), advanced cancer stage , metastasis and undernutrition before diagnosis as well as the extent of side effects of the specific protocols employed to treat the disease (Coates et al. 1986; Rickard et al. 1986; Rickard et al. 1983). Table 1.1 shows the cancer diagnosis associated with high nutritional risks for undernutrition during therapy.

However, there is not a single study aiming to assess the overall risk of undernutrition in paediatric cancer, many studies aimed to assess the prevalence of undernutrition at different stages of the disease as an indicator of nutritional risk. However, the interpretation of the data can be complicated due to the difference in nutritional assessment methods, study design, the type of cancer studied and the sample size used.

A cohort study (Reilly et al. 1999) reported an increased prevalence of undernutrition (BMI centile) at diagnosis in 1033 ALL patients compared to expected frequencies (Cole et al. 1995) (7.6 % boys and 6.7% of girls vs. 2.3 %). Similarly, a higher incidence of undernutrition (W/H percentiles, MUAC) at diagnosis was observed in 17 ALL patients in a case control study (Mejia-Arangure et al. 1997). This study stratified the patients according to disease severity (high risk (HR) ALL vs. low risk (LR). They reported an increased incidence of undernutrition in both groups compared to the general population with the HR ALL having a higher prevalence of undernutrition compared to the LR (17% normal population vs. 21% HR ALL and 24% LR ALL).

In contrast to the previous studies, other authors have failed to identify undernutrition at diagnosis in children affected by ALL (Delbecque-Boussard et al. 1997; Uderzo et al. 1996). For example, Uderzo and co- workers (1996) compared

Table 1.1 Cancer diagnosis associated with high nutritional risks for undernutrition during therapy (Betcher and Ablin 1993; Han-Markey 2000; Rickard et al. 1986)

Cancer type	Example
Brain tumour treated with radiotherapy	
Parameningeal, esopharingeal or oral tumours treated with radiation therapy	
Thoracic area tumours	Neuroblastoma, germ cell tumour, lymphoma, rhabdomyosarcoma, Ewing's sarcoma
Abdominal tumour involving the liver and gastrointestinal tract	Wilm's tumours, primary hepatic tumours
Pelvic tumours involving the gastrointestinal tract or requiring major operative procedures, pelvic radiation	Rhabdomyosarcoma, Ewing's sarcoma, Neuroblastoma, germ cell tumours
Solid tumours	
Advanced disease at diagnosis (stage III or IV) or relapse	
Acute non lymphocytic leukaemia, moderate and high- risk ALL, juvenile chronic myelogenous leukaemia, chronic myeloid leukaemia in blast crises.	

The prevalence of undernutrition (W, W/H, MUAC, and TSF) in 173 newly diagnosed Italian children with ALL to children affected by benign acute diseases as control. The study did not show any significant difference in prevalence of undernutrition between the two cohorts (6.9% ALL vs. 8.5 % with benign disease; $p>0.05$). Therefore, the authors concluded that the oncology cohort was not undernourished. However, the study had the methodological limitation of lack of comparison to the healthy population. Therefore, the similarity rate of undernutrition between the two groups could also be interpreted to be that both groups were undernourished. Furthermore, if the results are related to the other Reilly et al. study (1999) also carried out in the western world; the prevalence of undernutrition is similar. Therefore, the failure to detect undernutrition may be caused by the lack of comparison to population frequencies.

Although there is not a full consensus on the increased risk of undernutrition at diagnosis in ALL paediatric patients, the increased prevalence of undernutrition

among the solid tumour patients has been extensively reported (Garofolo et al. 2005; Jain et al. 2003; Rickard et al. 1983; Yaris et al. 2002). Garofolo et al. (2005) reported an incidence of undernutrition among 68 patients newly diagnosed with solid tumours ranging from 29.4 % to 45.6 % using respectively BMI and TSF measurements. Similarly, a more recent study (Jain, Dubey and Gupta 2003) evaluated the nutritional status of 44 children newly diagnosed with many types of cancer using haematological, anthropometric and biochemical indices. The prevalence of undernutrition varied depending on the criteria used and poor nutritional status overall was reported in 56.8 % of patients when using W/A criteria. These studies show that children with a solid cancer are at higher risk of undernutrition from diagnosis. The probable reasons for this are the metabolic changes caused by the tumours which may have persisted for a period of time before the cancer was diagnosed.

Evidence suggest that nutritional status can change dramatically during treatments in both solid (Yaris et al. 2002) and haematological tumours (Koskelo et al. 1990; Mejia-Arangure et al. 1997). For example, a study (Yaris et al. 2002) reported an overall increase in undernutrition rate among 47 paediatric patients affected by several types of cancer. At diagnosis the overall prevalence of undernutrition was 29.8%, after three months it increased to 38.5%. This study proposes a detrimental effect of treatments during treatment. However, the study did not stratify the patients according to diagnosis nor disease severity, probably because of the limited sample size. Therefore, the estimation of the risk of undernutrition based on specific diagnosis and disease severity is not possible.

Koskelo et al (1990) investigated the changes in nutritional status (muscle mass and weight) in children with ALL. They reported an extent of muscle wasting after four to six weeks of starting treatments in 27% of the 14 children in the study with no changes in body weight. Interestingly they also reported a parallel increase in FM which caused the weight and the limb circumference to stay the same as when first measured. These results highlight the importance of body composition in the assessment of nutritional status in this cohort.

Moreover, Mejia-Arangure and co-workers (1997) reported an increased rate of undernutrition during the course of treatments for ALL (three months). However, the nutritional status worsens only in the HR group. The Mejia-Arangure and co-workers (1997) study suggests that children treated for a high risk ALL are at an increased risk of undernutrition, probably due to both disease severity and more aggressive chemotherapy. Conversely, Delbeque–Boussand et al. (1997) failed to report any indication of undernutrition during the first three months of treatments. This lack of agreement is hard to explain and it is unlikely to be caused by the masking effect of steroids on body composition, since the authors assessed body composition by TSF.

In summary it has been widely recognised that nutritional status is likely to be affected by cancer at some point during the disease. However, the specific risk factors for the development of undernutrition have not yet been identified. The review of the literature showed that some phases of treatments may be at higher risk, however, the evidence on the specific phases in relation to specific treatment protocols is still unknown. In regard to the nutritional risk for obesity, some risk factors have been identified such as age at diagnosis, female gender, CRT treatments, steroid treatments and decreased PA. However, more studies are needed to determine the overall risk factors for the development of obesity, especially with the recent development in cancer treatments. Therefore, in order to design a specific screening tool for the oncology paediatric patients, it is now pivotal to identify the specific risks factors for both undernutrition and obesity during paediatric cancer and its treatments.

The overall aim of this series of investigations is to determine the risk factors for both undernutrition and obesity in childhood cancer. The specific aims and objectives of each single study are explained in the following sections.

2 CHAPTER TWO

THE NUTRITIONAL RISKS OF CHILDREN TREATED FOR CANCER: A RETROSPECTIVE STUDY

The poor nutritional status of children treated for cancer has been widely reported (Carter et al. 1983a; Carter et al. 1983b; Pietsch and Ford 2000; Smith et al. 1991; Uderzo et al. 1996). However, undernutrition in hospitalised children is often unrecognised and therefore left untreated (Agostoni et al. 2005). In the United Kingdom, the Paediatric Yorkhill Malnutrition Score (PYMS) (Gerasimidis et al. 2010) is used in some general paediatric populations as an inpatient screening tool, identifying those needing full nutritional assessment by a dietitian, and eventual NS.

NS comprises interventions to reverse or prevent undernutrition. It is important to assess nutritional status in order to use NS appropriately in children with cancer at high risk of the adverse effects of undernutrition at diagnosis and during cancer treatment. However, it is also pivotal, to avoid inappropriate increases in energy intake, given the later risk of development of overweight and obesity in some survivors of childhood cancer (Warner et al. 2002). However, no cancer-specific paediatric nutrition screening tool has been developed yet, and the use of a general paediatric screening tool is not appropriate as discussed in Chapter 1 . This lack of a specific screening tool is therefore a limiting factor for the improvement of nutritional management for paediatric oncology. This is because undernourished patients may be undetected and therefore not referred to the dietitian for nutritional assessment and nutritional intervention. Therefore, there is now a urgent need for the development of a specific paediatric cancer screening tool which is able to identify paediatric cancer patients at risk of both undernutrition and overnutrition.

In order to design a screening tool, studies including large numbers of participants are needed, often multicenter and even multi-country, which are very expensive, lengthy and complex. Preliminary research is therefore required to inform on what

are the risk factors for the development of undernutrition and obesity in this cohort, in order to then validate these in larger studies.

The aim of this retrospective study was therefore, to assess the prevalence of undernutrition during treatment for childhood cancer and identify the risk factors for undernutrition. In this retrospective cohort study, the use of NS during cancer treatment was used as proxy to indicate high nutritional risk. This is because, during cancer treatments actual weight can be affected by hydration status and tumour mass, masking body weight loss (Pietsch and Ford 2000; Smith et al. 1991). Since NS is initiated on the basis of a global assessment by the oncology multidisciplinary team and the hospital NS team,the use of NS as indication of nutritional risk overcomes the limitation of simple weight related measurements on underestimating undernutrition.

This study quantified the extent of clinical requirement for NS, and studied the relationship between NS usage,cancer type and treatment modalities. In addition, it aimed to identify subgroups within this population at highest risk of undernutrition with the intention to validate these findings in a prospective cohort. Furthermore, this study aimed to identify the prevalence of obesity in this cohort.

2.1 Aims and objectives

The aim of the retrospective study was to determine the prevalence of poor nutrition in children undergoing treatment for cancer, using the need for NS as a proxy for nutritional risk and to identify the risk factors for the late on-set of obesity.

The main objectives were:

- to quantify the extent of clinical requirement for NS;
- to study the relationship between NS usage and cancer type and treatment modalities in order to identify those within this population at high risk of undernutrition;
- to determine changes in nutritional status from diagnosis to the last clinical appointment;
- to assess the prevalence of overweight and obesity

2.2 Methods

2.2.1 Subjects and recruitment

Children < 18 years of age who were diagnosed with any type cancer between 2001 to 2006 and who were referred to the Royal Hospital for Sick Children, Edinburgh (the regional center in SE Scotland serving a population of 1.25 million) were included in the study. The study protocol was reviewed and approved by Queen Margaret University (QMU) Ethics Committee. Ethical approval from the NHS was not required after enquiry to the research ethics committee as the study fallen into the category of a retrospective audit of service design and delivery within this cohort. Patients' written consent was also not required for the above reason. The data for the prospective study remained anonymous and all the information collected remained confidential. Data was collected from medical notes and dietetic notes and entered into a database at diagnosis, end of treatment and last clinical appointment.

The data base was initially designed by Dr Laura Stewart and the data collection was partially carried out by Dr Laura Stewart, Ai Ling Koh and Huey Miin Lee. The author collected more information regarding NS, survival weight, and analysed the data.

2.2.2 Demographics

The demographics of the cohort were monitored and the following information was recorded; gender, date of birth; diagnosis date and survival at the final collection point (31/12/2011). Decimal age was calculated from date of birth at diagnosis and at every measurement by using the LMS Growth (Harlow Healthcare, UK) to allow growth comparison to the growth standards for the UK population (Cole, Freeman and Preece 1995).

2.2.3 Clinical information

Clinical information was collected from the medical notes. The type of tumour was classified using the international Classification of Childhood Cancer, Third Edition (ICCC-3) (Steliarova-Foucher et al. 2005).

Treatment protocols and treatment modalities were recoded in order to assess the nutritional risks according to treatments. However, because of the variability of treatment protocols available to treat childhood cancer, treatment modalities were

categorised into a broad groups with simpler parameters: chemotherapy only (with or without surgery); radiotherapy only (with or without surgery); chemotherapy and radiotherapy first line treatment (no recurrence); chemotherapy and radiotherapy (relapse treatment); surgery only; or no treatment.

2.2.4 Anthropometry

Growth was assessed by extrapolation of weight and height data from medical and dietetic notes at diagnosis, the end of treatments and last clinical appointment. Where appropriate, growth was also assessed at the initiation and end of NS. Where both the weight and height had been recorded, body mass index (BMI) SDS was calculated using the using the LMS Growth (Harlow Healthcare, UK) program with 1990 British growth reference values to assess undernutrition (Cole et al. 1995). In 2007, the Scientific Advisory Committee on Nutrition (SACN) and the Royal College of Paediatrics and Child Health (RCPCH) published a report on the use of the new WHO/UK growth standard (SACN/RCPCH 2007). In 2011 the new WHO/UK growth standards have been adopted for the monitoring of children 0-4 years old (RCPCH 2011). The new growth reference data includes children that closely reflect the current UK recommendation for infant feeding and they are believed to be more appropriate for growth monitoring (SACN/RCPCH 2007). However, for this retrospective study, the 1990 British growth reference values were used (Cole et al. 1995). This is because they were the standards used at the time of data collection and the clinical management of the children in the study was based upon these growth parameters. If height measurements were unavailable, BMI centiles could not be calculated. Therefore, undernutrition was defined as the SDS cut off point <-2SD of weight for age according to the WHO classification (World Health Organisation 2011)

There are no expected frequencies for the prevalence of undernutrition in the UK population assessed by using the weight <-2SDS definition. For this reason the prevalence of undernutrition in this study was compared against the 2.3 % value, which represents the -2SD for the general population. This figure is based on the rationale that 95% of the UK population is within the normal range, and it has been used elsewhere as expected frequency for comparison in paediatric cancer patients (Reilly et al. 1999).

Undernutrition was also assessed using the BMI centile ≤ 2.3th (SACN/RCPCH 2007) whenever both weight and height were available. The prevalence of undernutrition using BMI centiles was compared to the expected frequencies of 2% for undernutrition for female and male children combined, and 1.9% for boys and 2.1 % for girls (Scottish Government 2009).

In this study, where height and weight where available and BMI could be calculated, overweight and obesity were defined using the threshold for population monitoring as it is a standard UK government practice (Department of Health 2012). Overweight was defined as ≥ 85th / < 95th centile and obesity as ≥ 95th centile (Cole et al. 1995; Scottish Intercollegiate Guidelines Network 2010). These definitions are widely used in UK (Department of Health 2012) therefore it was decided to use this definition to maintain consistency and to allow comparison with the published literature. The prevalence of overweight and obesity was compared against the most recent Nutrition and Diet National Survey (Department of Health 2012). The NDNS was chosen over the Scottish Health Survey (Scottish Government 2009) because it distinguishes between overweight and obesity and it is the most recently updated survey.

2.2.5 Nutrition support

Information regarding the need for NS was recorded from clinical notes and dietetic notes. NS intervention was categorised as; use of oral calorie supplements (OCS); and/or enteral tube feeding (ETF) including nasogastric tube (NGT), gastrostomy tube (GT) or jejunal tube (JT); and/or parenteral nutrition (PN). 'Advanced NS' was defined as the need for ETF and/or PN.

Date of beginning and end of nutrition support and weight, weight SDS at initiation and end of nutrition support were recorded in order to assess the effectiveness of NS on improving nutritional status and/or preventing further nutritional deterioration.

2.2.6 Data analysis

Data were analysed with SPSS 19® (IBM®). Descriptive statistics are presented for this cohort in relation to demographic features, cancer diagnosis and its therapy, and use of NS.

The data were tested for normal distribution by the Shapiro-Wilk Test. The results are presented as mean (± SD) for normally distributed data and median (inter quartile range (IQR)) when not normally distributed.

For comparison according to gender (male vs. female) and diagnosis (solid vs. haematological) an Independent t- test was carried out. For comparison of the same group at two different time points a one sample t-test was carried out. The equality of variance was first tested by the Levene's test. If the test was not significant ($p>0.05$) equal variances were assumed. When the data where non-parametric comparison according to gender (male vs. female) and diagnosis (solid vs. haematological) was tested by the Mann-Whitney test. For comparison of the differences between before and after NS, the Wilcoxon signed-rank test was used.

When the data were analysed to test changes between measurements, a Kruskal–Wallis test was used. Difference between observed and expected frequencies of undernutrition, overweight and obesity were tested for significance using the Z test. The results were considered significant when $p<0.05$.

2.3 Results

2.3.1 Subjects

Between 1/12/2001 and 30/11/ 2006, 239 patients were diagnosed with childhood and teenage cancer. A flow diagram illustrating the composition of the cohort in terms of meeting the inclusion criteria is shown in Figure 2.1.

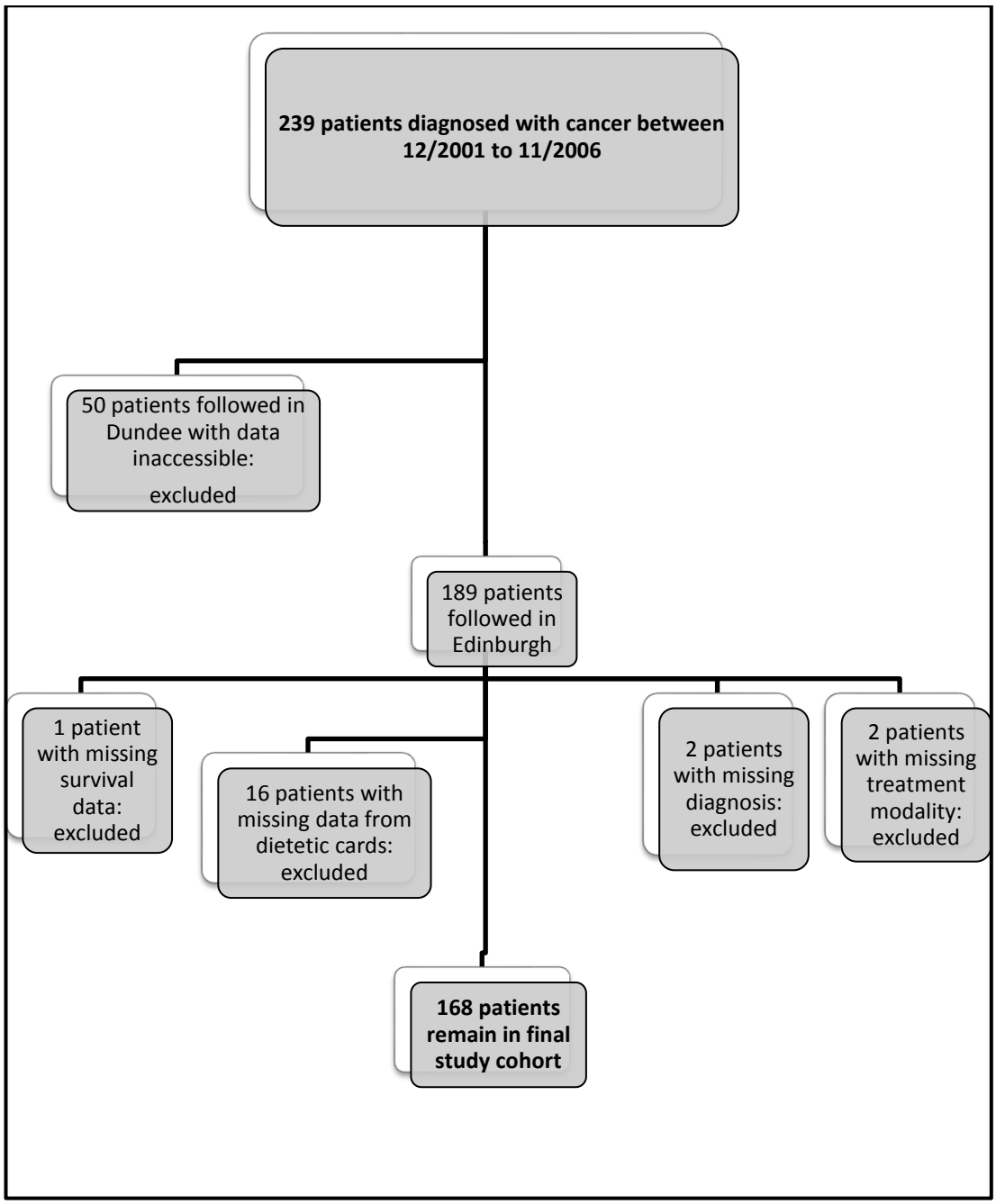


Figure 2.1 Diagram illustrating the composition of the cohort in terms of meeting the inclusion criteria

Ultimately, 168 (70%) of total patients were included in this retrospective analysis. All 50 (21%) managed mainly in Dundee were excluded. Of the 168 patients included, 81 were male (48%); the median age at diagnosis was 6.6 (IQR: 2.0-12.0) years. The overall survival rate at the end of the study period to 30/11/06 was 89% (n=149) and at the end of the monitoring period to 31/12/11 was 76 % (n=128).

Table 2.1 indicates the primary cancer diagnosis and the associated survival rate at the end of monitoring period of 31/12/2011.

Table 2.1 Primary cancer diagnosis and survival rate at end of monitoring period on 31/12/2011

Diagnosis	Cases (% within cohort)	Survivors (% with diagnosis)
I - Leukemia	**54 (32)**	**40(74)**
ALL	**45 (27)**	**37 (82)**
AML	**8 (5)**	**2(25)**
CML	**1 (1)**	**1(100)**
Solid tumours	**114 (68)**	**88 (77)**
II- Lymphoma	**18 (11)**	**17 (94)**
III -CNS tumour	**28 (17)**	**16 (57)**
IV- Neuroblastoma	**12 (7)**	**6(50)**
V- Retinoblastoma	**3 (2)**	**3 (100)**
VI -Renal tumour	**11 (7)**	**11 (100)**
VII -Hepatic tumour	**1 (1)**	**1 (100)**
VIII -Malignant bone tumours	**12 (7)**	**8 (67)**
IX- Soft tissue sarcoma	**14 (8)**	**14 (100)**
X -GCT	**7 (4)**	**6 (86)**
XI- Malignant epithelial neoplasm	**2 (1)**	**1 (50)**
XII- Others and unspecified malignat neoplasms	**6 (4)**	**5 (83)**

Of all 168 patients in the cohort, 112 (67%) received chemotherapy only, 21 (13%) received chemotherapy and radiotherapy (first line treatment), 13 (8%) received surgery only, 11 (7%) received chemotherapy and radiotherapy (recurrence treatment); 5 (3 %) received radiotherapy only; and 6 (4 %) received no treatment.

2.3.2 Prevalence of undernutrition at different time points

Weight was recorded at diagnosis for 152 (90%) of the 168 patients in the retrospective cohort. At the end of treatment, 17 children had died and weight was recorded for 105 (70%) of the remaining 151. Weight at the last clinical appointment was available for 127 patients. Mean (SD) weight SDS at each time point is shown in Table 2.2 according to diagnosis and gender. Comparison between gender and diagnostic groups showed that there was no significant difference in weight SDS at any time point ($p>0.05$ for all).

The prevalence of undernutrition at each time point was compared to the expected frequencies of undernutrition for the UK population to assess if the population in this

cohort had a higher prevalence of undernutrition than the general UK population (World Health Organisation 2011).

The comparison of undernutrition according to gender indicates an increased prevalence of undernutrition at treatment initiation for the male group ($p<0.05$) and during remission for the female group ($p<0.05$). Data analysed according to diagnostic group showed an increased prevalence of malnutrition at each time point for both diagnostic group ($p<0.05$) except for the haematological group at end of treatment (Table 2.2).

Table 2.2 Weight SDS, mean (SD) at each time point according to gender and diagnostic group

		Weight SDS mean (SD)	Prevalence of undernutrition % (n)	Confidence of intervals (CI) 95%	P value
Male	Diagnosis n=75	-0.03 (1.3)	9 (7)	0.025-0.155	<0.05
	End of treatment n=52	0.02 (1.2)	3.8 (2)	-0.014-0.090	N.S.
	Last clinical appointment n=52	0.96 (6.3)	2.0 (4)	-0.018-0.058	N.S.
Female	Diagnosis n=77	0.47 (2.9)	5.1 (4)	0.002-0.100	N.S.
	End of treatment n=53	0.29 (1.3)	0 (0)	0.000-0.000	N.S.
	Last clinical appointment n=75	0.6 (5.0)	7 (9)	0.003-0.137	<0.05
Solid	Diagnosis n=101	0.11 (1.3)	7.0 (7)	0.020-0.120	<0.05
	End of treatment n=81	0.08 (1.2)	2.5 (2)	-0.009-0.059	<0.05
	Last clinical appointment n=75	0.74 (5.3)	9.3 (7)	0.027-0.159	<0.05
Haematological	Diagnosis n=51	0.34 (3.4)	7.8 (4)	0.004-0.152	<0.05
	End of treatment n=24	0.25(1.3)	0 (0)	0.000-0.000	N.S.
	Last clinical appointment n=52	0.79 (6.3)	7.8 (4)	0.001-0.139	<0.05

2.3.3 The use of nutrition support

Because of the lack of recorded growth data and the potential masking effect of the cancer and treatments on weight loss (Pietsch and Ford 2000; Smith et al. 1991) NS was used as proxy of nutritional risk. Seventy four patients (44%) required NS during the period of the retrospective data collection. Forty patients (54% of all requiring NS) required OCS, ETF was required by 57 patients (77% of all requiring NS) and 32 patients (43% of all requiring NS) required PN. Of the patients requiring NS, 56 (76%) received NS through more than one route through the course of their treatment. Table 2.3 presents the use of NS according to specific cancer diagnosis. Fifty patients (68%) receiving NS had solid tumours, representing 44% of all children diagnosed with solid tumours during the data collection period. Twenty-four patients (32% of those receiving NS) had haematological malignancies, representing 44% of those with this diagnosis in the cohort. For all primary cancer types the highest needs for NS (where >50% required NS) were in CML at 100%, AML and neuroblastoma, at 75% (Table 2.3). Sixty-three (85%) of all those having NS required advanced NS (ETF and/or PN), of whom the neuroblastoma and bone tumour diagnostic groups had the highest needs (> 50% requiring advanced NS) at 67% each.

Table 2.3 Distribution of the use of nutritional support according to diagnosis

Diagnosis (n)	**NS cases (% total)**	**Frequency of route of NS**			**Advanced NS (% total)**
		OCS	**ETF**	**PN**	
I – Leukemia (54)	**24 (44)**	**16**	**21**	**12**	**22 (40)**
ALL (45)	**17 (38)**	**11**	**16**	**8**	**16 (36)**
AML (75)	**6 (75)**	**4**	**6**	**5**	**6 (75)**
CML (1)	**1 (100)**	**1**	**0**	**0**	**0 (-)**
Solid tumours (114)	**50 (44)**	**24**	**36**	**20**	**41 (36)**
II- Lymphoma (18)	**5 (28)**	**1**	**2**	**3**	**4 (22)**
III -CNS tumour (18)	**16 (57)**	**5**	**11**	**4**	**12 (42)**
IV- Neuroblastoma (12)	**9 (75)**	**5**	**8**	**6**	**8 (66)**
V- Retinoblastoma (3)	**1 (33)**	**0**	**1**	**1**	**1 (33)**
VI -Renal tumour (11)	**2 (18)**	**2**	**2**	**0**	**2 (18)**
VII -Hepatic tumour (1)	**0**	**0**	**0**	**0**	**0 (-)**
VIII -Malignant bone tumours (12)	**8 (67)**	**6**	**7**	**3**	**7 (58)**
IX- Soft tissue sarcoma (14)	**5 (36)**	**3**	**4**	**2**	**5 (36)**
X –GCT (7)	**2 (29)**	**1**	**1**	**2**	**2 (29)**
XI- Malignant epithelial neoplasm (2)	**1 (50)**	**1**	**0**	**0**	**0 (-)**
XII- Others and unspecified malignat neoplasms (6)	**1 (17)**	**1**	**0**	**1**	**1 (17)**

Of those 74 patients requiring NS, Table 2.4 describes the use of NS according to the treatment modalities received.

Table 2.4 Distribution of the use of nutritional support according to treatment modality

Treatment modality (n)	Nutrition support Cases (% of total)	Frequency of route of NS			Advanced NS (% of total)
		OCS	ETF	PN	
Chemotherapy (+/- surgery) (112)	**49 (44)**	**31**	**42**	**26**	**44(3)**
Chemotherapy and radiotherapy first line treatment (no recurrence) (21)	**10 (48)**	**5**	**9**	**2**	**9 (43)**
Chemotherapy and radiotherapy (recurrence treatment) (11)	**8 (73)**	**5**	**4**	**6**	**7 (64)**
Radiotherapy only (+/- surgery) (5)	**2 (40)**	**0**	**2**	**0**	**2 (40)**
Surgery only (13)	**1 (8)**	**0**	**1**	**0**	**1 (8)**
No treatment (6)	**0 (-)**	**0**	**0**	**0**	**0 (-)**

2.3.4 The effectiveness of nutrition support.

In an attempt to assess the effectiveness of NS on undernutrition, weight SDS was compared at the initiation and end of the period of NS. Of the 74 patients receiving NS, longitudinal data was only available for 22 patients, with median (IQR) weight SDS at the initiation and the end of NS being -0.73 (-1.55- 0.09) and -0.53 (-1.33- 0.13) respectively. There was no significant change in weight SDS for the 22 patients with available weight at initiation and end of NS over the period of NS ($p>0.05$)

2.3.5 Changes in BMI centiles from diagnosis to last clinical appointment

Changes in BMI centile were investigated to assess if this patients group was at higher risk of becoming obese. Only 18 patients had their BMI available at all three time points, hence statistical analysis was only possible for this limited number of patients. Changes in BMI centiles for these patients between measurements for patients (n=18) with BMI available at all three time points are shown in Figure 2.2.

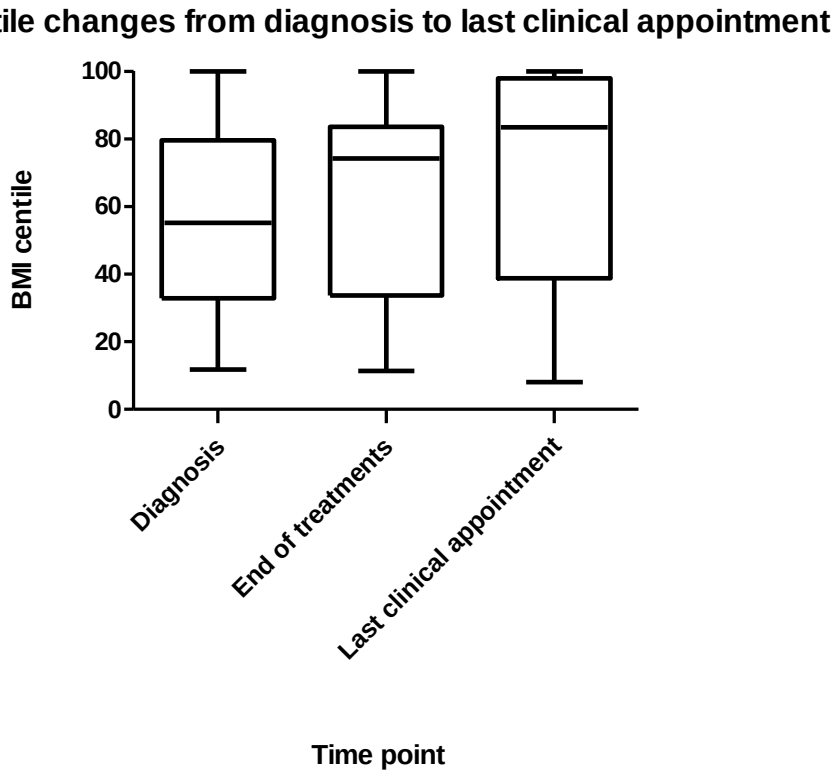


Figure 2.2 Changes in BMI centiles between measurements for patients (n=18) with BMI available at all three time points. p> 0.05

There was no significant change in BMI centile between the three points in time (p>0.05). Median (IQR) BMI centile did not differ between the male at diagnosis (49.9; 73.9-69.7); end of treatment (33.3; 61.9-38.8); last clinical appointment (67.3; 81.1-90.5) and female group at diagnosis (58.0; 75.4-88.7); end of treatment (38.1; 30.7-66.0); last clinical appointment (87.0; 91.9-98.3) at any measurements (p > 0.05 for all). Comparison of changes in mean BMI centile according to diagnosis was not possible because of the sample size. Only two out of 18 patients with BMI available

at all time points, had a haematologic diagnosis which did not allow statistical comparison.

2.3.6 Prevalence of overweight and obesity

The prevalence of overnutrition (≥85th centile) and obesity (≥95th centile) at each time point was compared to the expected frequencies for the UK population (Department of Health 2012) to assess if the population in this cohort had a higher prevalence of overweight and obesity that the general UK population. The prevalence of overweight and obesity at each time point is shown in Table 2.5 as numbers and percentage of the entire cohort.

Table 2.5 Prevalence (%) of overweight (BMI ≥ 85th / < 95th centile centile) and obesity (BMI ≥ 95th centile) at each study time point

	Overweight n (%)	**Obesity n (%)**
Diagnosis n=59	7(12)	5 (8)
During treatments n=73	12 (16)	13(18)
Last clinical appointment n=95	18 (19)	20 (21)

The observed rates of classification of children as overweight did not differ ($p>0.05$) from the expected frequencies of 15% (Department of Health 2012) at any measurement point. Similarly, the observed frequencies of obesity did not different to the expected frequencies of 18.5% (Department of Health 2012) at any measurement ($p>0.05$) apart from at diagnosis where they were significantly lower ($p<0.05$; 95% CI 1.0% to 14.9%).

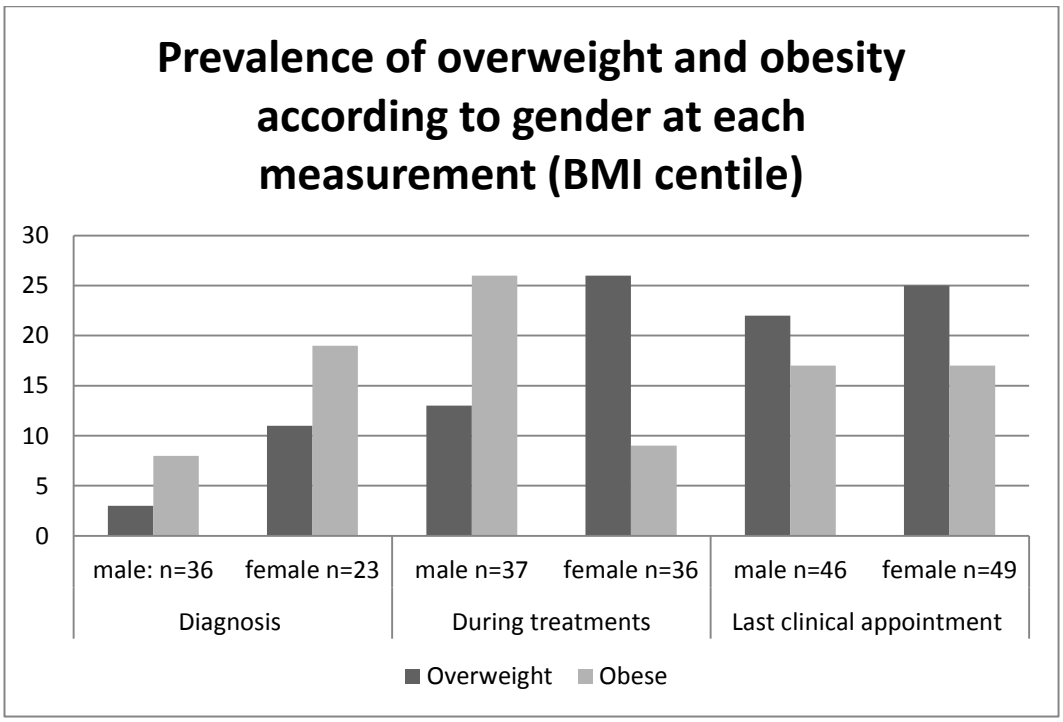


Figure 2.3 Prevalence of overweight (BMI ≥ 85th/ <95th centile), obesity (BMI ≥ 95th centile), according to gender at each measurement presented as percentage of patients with BMI available.

The prevalence of overweight and obesity at each measurement according to gender is shown in Figure 2.3. The observed occurrences of males classified as overweight were significantly lower ($p<0.05$) than the expected frequencies of 15% (Department of Health 2012) at diagnosis. There was not a significant difference at any other measurement for both overweight and obesity prevalence for both genders ($p>0.05$ for all).

The prevalence of overweight and obesity was assessed according to diagnosis in order to identify those cancer types at higher risk of overnutrition (Table 2.6).

Table 2.6 Prevalence of overweight and obesity according to diagnosis at each study time point presented as percentage.

	Diagnosis n (%)		End of treatment n (%)		Last Clinical appointment n (%)	
	overweight	**obese**	**overweight**	**obese**	**overweight**	**obese**
Haematological: n= 4, 21, 29	**-**	**-**	**7 (33)**	**6 (29)**	**7 (24)**	**5 (17)**
Solid: n= 55, 52, 95	**7 (12)**	**5 (9)**	**5 (10)**	**7 (13)**	**11 (12)**	**15 (16)**

For all primary cancer types the highest prevalence of overweight and obesity was found in the haematological group at end of treatment with 33% of the patients being overweight and obese respectively. There was no significant difference between the observed frequencies of overweight and obesity according to diagnosis to the expected frequencies for the UK population (Department of Health 2012) ($p>0.05$ for all).

2.4 Discussion

This retrospective cohort study from a regional UK paediatric haematology-oncology service provides the first longitudinal clinical observations on nutritional risk, as determined by the usage of NS in children and adolescents treated for childhood cancer. It was not possible to find comparable data available in the literature on the use of NS in paediatric cancer patients; therefore, this is the first study to measure the extent of use of NS in this patient group. Although retrospective, this cohort study has the strengh of containing all types of childhood cancer. This study showed a marked risk for the development of undernutrition during childhood cancer therapy, with almost half of the patients requiring NS at some point during their treatment.

The most common diagnosis in this retrospective cohort was leukemia followed by the CNS tumours, lymphoma, and soft tissue sarcoma. The distribuition of each type of childhood cancer appears to reflect the distribuition in the UK population which is shown in Chapter 1 (Cancer Research UK 2012) suggesting that this cohort is

representative of the UK childhood cancer population as a whole. The average survival rate over five to ten years was 76%, with leukemia, renal tumours, and lymphoma having the highest rates of survival. The survival rate of each type of cancer reflected the survival rate in the UK population which is shown in Chapter 1 (Cancer Research UK 2012).

2.4.1 Assessment of undernutrition based on height and weight parameters

Although weight at diagnosis through to the last clinical appointment was well recorded, recording of height during both clinical assessment and dietetic assessment was lacking. A similar lack of height recording in routine clinical practice has been recently reported in a multicentre UK paediatric nutrition survey (Carey et al. 2011). Therefore, in both that survey and this cohort study, it was not possible to calculate the BMI for most of patients and weight SDS was used in this study to assess undernutrition.

The comparison to the prevalence of undernutrition for the general population (World Health Organisation 2011) showed an increased risk of undernutrition for both diagnostic groups at all time points, apart from the haematological group at the end of treatment. The lack of undernutrition at end of treatment observed in the haematological group may be explained by the transient weight gain in response to steroid therapy. When the cohort was stratified according to gender, it became apparent that boys have a higher risk of undernutrition at diagnosis, whereas for girls risk is higher during remission phase. It was concluded that patients treated for cancer are at increased risk of undernutrition throughout the treatments.

However, the limitation of missing BMI data and the use of weight <-2SDS to measure undernutrition prevented the precise quantification of the prevalence of undernutrition in this cohort.

Because of limited height recording, it was not possible to analyse the prevalence of undernutrition using BMI centiles. It is not clear whether the patients with BMI available represented the entire cohort in this study as a whole. The reasons for the recording of height for some patients and not for others are unknown. One of the possible explanation is the change in clinical practice after the RHSC audit in 2003

(Holt 2003) where a lack of appropriate nutritional assessment in children treated for cancer emerged. After the audit was completed in 2003, the nursing and medical staff was required to start recording height and weight of the patients more regularly. Since this retrospective study includes all patients treated between 2001 and 2006, it is likely that the patients treated and/or diagnosed after 2003 had their height monitored more closely than those treated and diagnosed before the audit. Another possible explanation may be that the recording of height has reflected a closer monitoring of children with nutritional issues. However, this seems to be unlikely since many dietetic cards did not have the patient's height recorded and anthropometrical assessment of NS was done by weight alone.

Furthermore, obesity was significantly lower at diagnosis for the entire cohort. A weight loss greater than 5% in a month is considered a sign of nutritional deprivation even when the patients is not classified as undernourished by anthropometrical parameters (Jeejeebhoy and Keith 2005). This is because an obese or overweight patient in negative energy balance may need to loose extensive amount of weight before they are classified as underweight by anthropometric cut off points. Therefore, a decreased prevalence of obesity at diagnosis could indicate the extent of nutritional deprivation and support further the increased risk of undernutrition at diagnosis as previously reported (Garofolo et al. 2005; Reilly et al. 1999; Yaris et al. 2002).

Unfortunately, the literature is lacking in any comparable paediatric haematology-oncology study on the prevalence of undernutrition in the developed world after the year 2000. The rate of undernutrition for the general population varies dramatically between countries. The undernutrition rate reported in some studies (Lobato-Mendizabal et al. 1989) must be interpreted in relation to the regional prevalence of undernutrition and may not be relevant for this current study. Furthermore, because of the constant progresses in paediatric cancer treatments, the research published before our data collection period may be not suitable for comparison with the prevalence of undernutrition documented in this current study.

Additionally, other studies on the prevalence of undernutrition in childhood cancer may be limited by being of relatively small sample size (≤25)(Kibirige et al. 1987;

Yu et al. 1994), or of cross-sectional study design with the incidence of undernutrition determined only once during treatment (Pietsch and Ford 2000; Smith et al. 1991; Uderzo et al. 1996). Moreover, some studies were conducted only on a specific cancer diagnosis (Uderzo et al. 1996; Yu et al. 1994), and using differing methods for assessing the prevalence of undernutrition such as BMI, TSF and MUAC (Oguz et al. 1999; Pietsch and Ford 2000; Smith et al. 1991). Comparison of results on the prevalence of undernutrition between our cohort and other studies of paediatric cancer is therefore difficult.

The lack of recorded height data in this study was a limitation as it did not allow the calculation of BMI for the entire sample. Any retrospective analysis of clinical data relies on the parameter of interest, in this case NS, not being a focus when the data was originally collected. Despite awareness of the importance of nutrition in the course of childhood cancer, neither the capture nor monitoring of NS was fully embedded into routine clinical care at the RHSC from 2001-2006. However, after the audit in 2003 and the findings of this study, more constant and comprehensive monitoring of growth is now in place. This lack of available anthropometric data had prevented the analysis of the impact of both childhood cancer and its treatment on nutrition and growth. Furthermore, it did not allow full evaluation of the long term risk of developing obesity in this cohort.

2.4.2 Nutrition support as proxy of nutritional risk

The extent of use of NS in relation to cancer diagnosis and treatment modalities has not been previously described in children. The advantage of using the need for NS as proxy to indicate nutritional risk is that it overcomes the limitation of some simple anthropometric methods on assessing nutritional status, given that many can underestimate undernutrition (Smith et al. 1991; Uderzo et al. 1996). NS is initiated on the basis of a global assessment, including weight loss, energy and nutrient and fluid intake, gastro-intestinal and other symptoms, and treatment severity by the oncology multidisciplinary team and the hospital NS team. As such, it may provide a better indication of nutritional risk in this group. Although if NS is started on a prophylactic or preventive basis rather than on a treatment basis this may indicate perceived risk rather that actual risk.

Remarkably, this study showed that a high proportion of children receiving some type of NS required the most advanced nutrition support treatment. This indicated the great extent of nutritional depletion. Although almost half of the children received at least one type of NS, the data showed that within groups with both solid tumours and haematological malignancies, it is specific types of cancer which are associated with a particularly high risk of undernutrition. In particular, 100% of those with CML, 75% of those with AML and neuroblastoma, 67% of those with malignant bone tumours, and more than 57% of patients with CNS malignancies required NS. Although 100% of patients with CNL required NS, only one patient was diagnosed with CML in our cohort, therefore, it is not possible to draw any conclusion on the nutritional risk for this type of leukaemia. Furthermore, 66% of those with neuroblastoma and 58% of those with malignant bone tumours required advanced NS, confirming that these types of cancers result in the highest nutritional risk. This reflects the intensity of the treatment (duration and intensity of chemotherapy). Although ALL, the commonest tumour in children, requires treatment for two years for girls and three years for boys, the intense treatment phase is short in contrast to the six to nine months of intense treatment for bone tumours, or high dose therapy for neuroblastoma. These observations reflect the spectrum of diagnosis associated with greater risk of undernutrition in the literature (Betcher and Ablin 1993; Han-Markey 2000; Rickard et al. 1986). These results may be important when considering targeted and enhanced nutritional monitoring to ensure that patients known to be at a high risk of undernutrition are correctly identified, although the breadth of diagnoses requiring nutrition NS in this cohort suggests that comprehensive monitoring is necessary.

Consideration of the extent of use of NS in relation to the treatment modalities indicated that the highest usage was among children receiving chemotherapy, and radiotherapy (recurrence treatment) followed by those receiving chemotherapy, and radiotherapy as first line treatment and chemotherapy with or without surgery. The lowest usage appeared to be amongst children receiving radiotherapy only, with or without surgery, and surgery only. The detrimental effects of radiotherapy vary depending on the length and dose of irradiation as well as the irradiated area, with abdominal pelvic and cervical area being at higher risk (Donaldson 1977; Piquet et

al. 2002). Unfortunately, the lack of recorded data on the location and dose of radiotherapy in this study made it impossible to determine the specific effect of these variables on nutritional deterioration.

These results suggest that there appears to be an increased risk of undernutrition in relation to some treatment modalities, in particular chemotherapy. It is not clear whether this is a reflection of the diagnosis itself, the treatment modality alone or, more likely, a combination of both. Moreover, the treatment modalities for childhood cancer are very complex and heterogeneous, with many different regimens being employed for each cancer diagnosis. For example, the treatment category of chemotherapy with or without surgery comprised many different treatment protocols and therefore it was not possible to identify specific associations between aspects of the treatment and nutritional implications. Treatment modalities for childhood cancer advance with time and the current treatment modalities in 2012 may be different from those in the time span analysed in this study (2001-2006).

A limitation of this study was the impossibility of distinguishing between the use of NS as prophylactic treatment to prevent nutritional depletion and the use of NS as nutrition treatment. The current dietetic practice at the RHSC Edinburgh is to start nutrition support in those patients treated with protocols likely to cause nutritional depletion (bone cancers are the main example) even when they are not undernourished. However, this decision is made on a subjective basis and after a global assessment and it is not recorded in the patients' clinical notes. Therefore it was not possible to distinguish those in prophylactic treatments from those who were not. However, NS is generally stopped if the patients do not develop the nutritional side effects of the treatments; consequently it is very likely that those who were classified as undernourished by the use of NS as a proxy of undernutrition were truly at nutritional risk.

2.4.3 Effectiveness of NS in counteracting undernutrition

In the present study no significant difference was seen between mean weight SDS at initiation and at end of NS, which suggests the positive effect of NS on preventing further nutritional deprivation but not on improving nutritional status. However, only a limited number of patients within this cohort had weight SDS available at both

time points, which makes the interpretation of these results difficult. The observed effect of NS on preventing further nutritional deterioration but not on improving nutritional status could be therefore, attributed to a closer monitoring of patients at higher nutritional risk, rather than NS being ineffective in counteracting undernutrition per se.

Even though NS is widely used in children with undernutrition, its effectiveness to counteract cancer-related undernutrition remains unclear. Some studies have shown a positive effect on undernutrition (den Broeder et al. 1998; den Broeder et al. 2000; Rickard et al. 1979; Smith et al. 1992) whereas others (Rickard et al. 1985; Rickard et al. 1989) found NS to be ineffective in counteracting undernutrition. This inconsistency may be explained by the small number of patients studied, differences in cancer diagnoses, and methodological limitations. For example, few studies were randomised controlled trials (den Broeder et al. 1998; Smith et al. 1992), and some studies (Rickard et al. 1979; Rickard et al. 1985; Rickard et al. 1989) are now very dated. This is particularly relevant since the recent improvement in management of nausea and vomiting is likely to have increased tolerance to ETF and therefore improved the effectiveness in counteracting undernutrition, as shown in later studies (den Broeder et al. 1998; den Broeder et al. 2000; Smith et al. 1992).

2.4.4 Overweight and Obesity

Obesity in children is usually not assessed by weight for age because obesity depends on both height and weight. Although BMI centiles in children do not necessarily reflect body composition and its changes (Scottish Intercollegiate Guidelines Network 2010), there is evidence to support the use of BMI centiles to define obesity in this population group (Cole et al. 1995; Scottish Intercollegiate Guidelines Network 2010). Therefore, only BMI centiles were used to assess overnutrition in this cohort. Hence, the prevalence of overweight and obesity could only be assessed for those patients with height available to calculate BMI.

Although not significant, this current study showed a trend towards an increase in BMI centiles from diagnosis to remission. Furthermore, it showed a higher prevalence of overnutrition compared to the UK population at end of treatment and last clinical appointment, particularly in girls. When the cohort was stratified

according to cancer diagnosis, it was observed that the highest prevalence of overnutrition was among children with haematological tumours at the end of their treatment. Although not statistically significant, quantitative comparison to the excepted frequencies of overweight and obesity for the UK population showed an increased risk at end of treatment and last clinical appointment in the haematological group.

The observed increased in BMI centile overtime may be explained by both/either an improvement in nutritional status of patients during the data collection period and/or excess body weight gain. However, if the prevalence of undernutrition and overnutrition observed in this study are considered, it appears that no patient was classified as undernourished at any measurements. Nevertheless, it is likely that, although not statistically significant, children in this cohort experienced excessive weight gain.

The small sample size of those patients with BMI available is likely to have affected the statistical analysis and to have caused of the lack of significance. However, is not clear whether the data were randomly missing or if there was a particularly reason for the increased nutritional monitoring in those patients as, for instance, more attention given to those patients with nutritional issues. Furthermore, the data in this study were compared to the NDNS (Department of Health 2012) which represents the whole UK and it may did not take into account the differences in regional prevalence of obesity. However, when the data for obesity and overweight as a whole from the NDNS 2011 (Department of Health 2012), are compared to the figures from the Scottish Health Survey (SHS) (Scottish Government 2009) for both genders , the data from the NDNS (Department of Health 2012) were slightly lower that the SHS 2008 for boys (33% vs. 36% respectively) but much higher for girls (34% vs.26.9% respectively). Therefore, if the data for the females in this current study was compared to the Scottish Health Survey (Scottish Government 2009) instead of the NDNS 2011 (Department of Health 2012) , it would have resulted on a even higher increase on the prevalence of overweight and obesity.

The trend towards excess weight gain after childhood cancer treatment observed in this study is supported by previous research, which has extensively shown an

increased risk for the late onset of obesity in children treated for ALL and cranyopharingioma (Dalton et al. 2003; Meacham et al. 2005; Oeffinger et al. 2003; Warner et al. 1995). Furthermore, the observed increased risk for girls in this study has been reported in several other studies (Gurney et al. 2003; Jarfelt et al. 2005; Warner et al. 2002), even though the reasons for this sex related risk is still unknown.

These results suggest that there appears to be an increased prevalence of overweight among ALL, lymphoma at end of treatment and CNS patients in remission. The association between these three cancer types and the later obesity has been previously reported (Nysom et al. 1999; Oeffinger et al. 2003; Razzouk et al. 2007; Schell et al. 1992; Muller et al. 1998; Nysom et al. 2003). However, comparison of the prevalence of obesity observed in this cohort and those reported in the haematology-oncology studies is complex because of the different methodologies used to assess obesity in the literature. For example, most of the studies were carried out only in childhood ALL survivors (Meacham et al. 2005; Sainsbury et al. 1985; Schell et al. 1992; Zee and Chen 1986). Moreover, some authors used the cut off points of BMI >25 and >30 Kg/m^2 to adults to define overweight and obesity in their study (Schell et al. 1992; Warner et al. 2002) which are not recommended in children because of the body composition changes during growth the dependence on gender (Scottish Intercollegiate Guidelines Network 2010).

The literature suggests many risk factors for the late development of obesity such as, age at diagnosis (Dalton et al. 2003) CRT , chemotherapy (Odame et al. 1994; Oeffinger et al. 2003; Reilly et al. 2001), fat overshooting (Dulloo et al. 2012) and early adiposity rebound (Reilly et al. 2001b). Unfortunately, it was not possible to determine the reasons for the increased prevalence of obesity observed in this study. The lack of recorded height and weight did not allow the calculation of BMI for many patients making it impossible to analyse the data in relation to the variables believed to play a role in the development of obesity such as for instance steroid therapy or age at diagnosis.

Furthermore, it is not clear whether the extent of the starvation state in children during treatment for cancer is enough to lead to fat overshooting (Dulloo et al. 2012)

causing the patient's weight to exceed the pre-illness weight. In this current study, pre-illness weight was not available; therefore it was not possible to compare weight in remission with pre-illness weight to demonstrate whether the patients were overshooting their set-point or not.

This current study suggests a trend towards excess body weigh as long term consequence of childhood cancer. This is particularly worrisome given the fact that it is likely that the presence of excess body weight will be carried into adulthood with the consequent increased the risk for CVD , diabetes and reduced quality of life (Sinaiko et al. 1999). Clearly, elucidation of the mechanisms involved in this excess weight gain and the identification of treatment protocols and cancer types at higher risk have important implications for the long term management of those children identified at great risk.

2.5 Conclusions

This research was a preliminary step towards identifying the risk factors for malnutrition in childhood cancer. This retrospective analysis assessed the incidence of undernutrition in this cohort, using the need for NS as a proxy for high nutritional risk, and the relationship of NS usage to cancer type and treatment modalities. These findings underlined the common need for NS in this childhood cancer cohort, and also indicated apparent differences in nutritional risk according to diagnosis and treatment.

Despite awareness of the importance of nutrition in childhood cancer, the lack of comprehensive longitudinal growth and nutrition support would suggest that clear guidelines for monitoring are urgently required. Use of an appropriate screening tool would not only allow early identification of those at risk of undernutrition, but would also serve to guide monitoring of the effectiveness of NS. In order to develop a comprehensive screening tool specifically for use in this population, it is essential to conduct a large prospective cohort study to monitor nutritional status in children with cancer from diagnosis through to the end of treatment. These findings could identify the factors that influence nutritional status and facilitate clinical guidelines for the routine monitoring and assessment of risk. The development of a screening tool would allow early and effective nutritional intervention to reduce the risk of

nutritional problems in children with cancer throughout the course of the disease and its treatment.

This retrospective study aimed to identify those children and young people treated for cancer at risk of nutritional problems and the important parameters to determine nutritional risk with the intention to initially validate those findings in the prospective cohort. However, because of the lack or recorded height and weight it was not possible to do so. Therefore, instead of validating the findings from the retrospective study, the prospective study was carried out aiming to monitoring paediatric cancer patients to identify factors influencing nutritional risk.

3 CHAPTER THREE

PILOT STUDY: 'ASSESSMENT OF RELIABILITY AND PRECISION OF ANTHROPOMETRICAL MEASUREMENTS PERFORMED IN HEALTHY CHILDREN'.

The prospective study was designed to longitudinally assess the nutritional status of children and teenagers treated for childhood cancer. The prospective monitoring of nutritional status included regular anthropometric measurements to assess growth (height, weight and BMI) and body composition (MUAC and TSF). Both random and systematic errors can occur in anthropometrical measurements which may affect precision and reliability (Atkinson and Nevill 1998; Jamaiyah et al. 2010; Ulijaszek and Kerr 1999).

Random errors may limit the degree to which repeated measurements provide the same value (Gibson 2005). High precision corresponds with low variability in successive measurements and it indicated a high probability that the measurement is close to the true value (Gore et al. 1996). Random measurement errors can be minimised by the use of standardised protocols, a single trained observer and suitable and calibrated equipment (Jebb and Elia 1993). However, such errors can never be completely eliminated (Gibson 2005), therefore the precision and reliability of the measurement must be established prior to the research. This strategy will allow the error to be accounted for when interpreting the data.

The precision of measurements can be calculated by quantifying the technical error of measurement (TEM) and the %TEM, which overcomes the difficulty of TEM being dependent on the size of original measurement. It has been suggested that the % intra-observer error for a beginner is acceptable when it is below 1.5% (Ulijaszek and Kerr 1999). Reliability is calculated by measuring the Interclass Correlation Coefficient (ICC), and indicates the proportion of between-subject variance in a population which is free from TEM (Gibson 2005). It describes how strongly measurements in the same group resemble each other. An ICC of 0 is classified as

not reliable and not valid, whereas an ICC equal to 1 is considered highly reliable and valid (Atkinson and Nevill 1998; Jamaiyah et al. 2010; Ulijaszek and Kerr 1999).

None of the studies that aimed to assess nutritional status using TSF and MUAC (Garofolo et al. 2005; Oguz et al. 1999; Smith et al. 1991) calculated the TEM and the ICC, making the precision and reliability of the measurement questionable.

In general the precision of weight and height measurements is high; however, the precision of anthropometrical measurements is highly dependent on the researcher's skills. Training and the use of standard techniques are critical. Moreover, the degree of error and inaccuracy must be minimised and accounted for when interpreting the data. For the purpose of the prospective study it was essential that the techniques of measurements were optimised and the TEM and ICC calculated.

3.1 Study aim and objectives

The aim of the study was to asses the reliability and precision of the anthropometric measurements used in the prospective study (see Chapter 4). Therefore, the intra-observer of technical error (TEM) and interclass correlation coefficient (ICC) were measured.

The objective of the pilot study was:

- To quantify the intra-observer TEM and ICC for height, weight TSF and MUAC.

3.2 Materials and methods

3.2.1 Study population

The literature suggests a minimum of ten children, including both genders (Ulijaszek and Kerr 1999), to be included in the study to assess the ICC and TEM. Furthermore, since TEMs vary according to target population, the cohort incorporated in the pilot study should reflect the age of the study cohort (Norton and Olds 1997). However, since the study aimed to assess the reliability and precision of the researcher technique, it could be carried out on healthy children. Hence the inclusion criteria for the study were any healthy child and adolescent between the age of 1 and 18.The

exclusion criteria were children younger than 1 year or older than 18 years of age, children with any medical conditions.

Even though children younger than one year of age were to be included in the prospective study, their length measurement at the hospital was taken by the nursing stuff. Furthermore, for safety, the arm measurements require the use of the cot, which was not available at QMU. Considering that, the input on assessing the TEM and ICC would have been minimal, and due to the practical and safety issues of measuring babies, it was believed that their exclusion was preferable.

The participants were recruited by the QMU moderator email system. Written and oral age- appropriate information were given to both parent and child (Children 6 to 11 were given the children's information sheet and those older than 11 the adult's one) (Appendix 4). A period of time to consider about taking part to the project was given to both parent and child. Afterward, both parents and child were asked if they agreed to participate. Only if both the parent and the child agreed, the recruitment took place. The measurements where taken on one occasion at QMU. The study had ethical approval from QMU Ethics Committee (Appendix 1).The data were coded with an identification number to ensure anonymity. The raw data were stored at QMU.

3.2.2 Anthropometrical measurements

Age and gender were recorded for each participant. Height was measured using the wall-mounted stadiometer (SECA Hamburg, Germany) available at QMU. The participant was measured without shoes and thick socks and he/she was positioned to touch the back plate with his/her back, heels and buttocks. The head was positioned to look straight ahead with the lower border of the boney orbit and the upper margin of the external opening of the auditory canal in the same horizontal line. The child was asked to breathe in while supporting the head in the right position and then asked to breathe out. The measuring board was placed on the top of the head and the height recorded. Height was measured to the nearest 0.1 cm

Children were weighed without shoes, in light clothing, on the standing scales available at QMU SECA 599 (SECA Hamburg, Germany).Weight was measured to the nearest 0.1 kg.

The TSF measurements were taken by the same investigator, on the non-dominant arm half way between the olecranon and acromion by a skinfold caliper (Holtan LtD. Crymych, UK) for each subject. The measurement was taken by pulling the skin and adjacent subcutaneous tissue between the thumb and the forefinger away from the muscle tissue far enough to allow the caliper to be placed. The measurement was taken once to the nearest 0.2 mm at the marked arm midpoint.

The MUAC was measured by the same investigator three times from the non-dominant arm half way between the olecranon and acromion with a non stretchable measuring tape (Holtan LtD. Crymych, UK) to the nearest 0.1 mm. The measurements were taken once at the marked arm midpoint.

The full set of measurements was taken two times.

3.2.3 Data analysis

The intra-observer TEM and %TEM for the set of anthropometrical measurements were calculated as follows (Ulijaszek and Kerr 1999). The mean of the two measures, for each anthropometrical measurement were compared by a two-way ANOVA to test for any significant difference between the means.

The following equations were then used to calculate both TEM and %TEM

TEM= √ error mean square

% TEM = (TEM/mean) x 100

ICC is the correlation coefficient (r) and it measures reliability. It functions on data organized as groups, rather than data organized as paired observations (Field 2009). ICC was calculated using the One-way random single measures test available in SPSS®.

3.3 Results

3.3.1 Study population

A total number of ten children were recruited for the pilot study, 50% were female and 50% were male. The median age was 8.5 (IQR 6.5, 10.7) years.

3.3.2 TEM and ICC

There was no significant difference between the means of the two measurements for height, weight, TSF and MUAC. Therefore TEM, %TEM and ICC could be calculated for each anthropometrical measurement (Table 3.1)

Table 3.1 TEM and ICC

	Height	Weight	TSF	MUAC
F	0.00	0.00	0.02	0.00
p value	1	0.99	0.97	0.99
TEM cm	0.02	0.02	0.17	0.12
TEM%	0.06	0.02	1.3	0.6
ICC	0.99	0.99	0.94	0.96

3.4 Discussion

The TEM indicates that the true value of the subject at 68% of confidence interval is included between the measurement ± TEM. The technical errors estimated from the pilot study, are below the acceptable value of 1.5% and they were comparable to the target TEM for the accreditation level 2 post-course anthropometrist (Gore et al. 1996) for both MUAC and TSF.

The one way ANOVA of the data with two measurements of weight, height, TSF and MUAC showed a high level of agreement. It is therefore permissible to assume that the measurement procedures will have a high level of reliability.

3.5 Conclusions

The assessment of precision and reliability demonstrated a high level of reliability and a small measurement error. Therefore, it is permissible to assume that the researcher is able to detect with confidence anthropometrical changes. The technical error of the measurement and the ICC will be taken into consideration when interpreting the data from the prospective study.

4 CHAPTER FOUR

THE NUTRITIONAL RISKS OF CHILDREN TREATED FOR CANCER: A PROSPECTIVE STUDY

The findings from the retrospective study showed that children treated for cancer are at high risk of nutritional depletion and it indicated apparent differences in nutritional risk according to diagnosis and treatment modalities. However, the lack of comprehensive growth and nutritional status monitoring during paediatric cancer treatments in this centre from 2001-2006 prevented the identification of important parameters to determine nutritional risk. Therefore, it was not possible to validate these findings in the prospective cohort as intended. Thus, instead of validating the findings of the retrospective study, the prospective study was carried out aiming to monitor paediatric cancer patients to identify factors influencing nutritional risk.

This single centre prospective study provides the exceptional opportunity to investigate factors contributing to the development of malnutrition in children and teenagers treated for cancer.

4.1 Prospective study aims and objectives

The aim of this study was to investigate factors contributing to the development of malnutrition (obesity or undernutrition) among children with cancer.

The main objectives were

- To prospectively monitor changes in nutritional status indices (BMI, growth, body composition and blood parameters) from diagnosis through the progression of disease in response to treatments, and nutritional intervention.
- To prospectively follow for 18 months a cohort of children newly diagnosed with cancer to assess determinants for the development of undernutrition.
- To prospectively follow for 18 months a cohort of children newly diagnosed with cancer to assess early determinants for the development of overnutrition.

- To prospectively follow micronutrient status in response to treatments and nutritional intervention.
- To evaluate the effectiveness of NS in maintaining or improving nutritional status and counteracting undernutrition.

4.2 Methods

The study design aiming to explore the nutritional issues and risks involved in paediatric oncology followed a descriptive quantitative research method.

The prospective study had ethical approval from NHS Scotland (NHS REC 06-51104-52) until Dec 2012 (Appendix 2). Ethical approval was not required from QMU Ethics Committee as the project had secured ethical approval from the NHS (Appendix 3). The researchers working on this project had the relevant enhanced disclosure enabling them to work with this population.

Patient data remained confidential and all data was anonymised.

4.2.1 Subjects and recruitments

The cohort consisted of all children diagnosed with any type cancer and benign brain tumour between August 2010 to December 2011 at the Royal Hospital for Sick Children, Edinburgh, the regional centre in SE Scotland serving a population of 1.25 million.

Patients in palliative care and those patients not receiving ongoing care where excluded from the study. Moreover, those patients who were recruited and became palliative during cancer treatments, were withdrawn from the study as soon as they were confirmed palliative by the consultants.

The child and the parents or guardians were provided with full written information regarding the project to give them the opportunity for ‘informed consent’ and given at least 24 h to think about the project before making the decision to take part to the study or not. The information were given orally and in a written format explaining what the study involved, the possible consequences for the child and that the child was not under any type of obligation to take part to the study, and he/she may withdraw at any time. Furthermore the child and the parents or guardians were given

the opportunity to take part in all or any parts of the study that they wished. Written consent was obtained from all parents and children.

4.2.2 Demographics

The cohort was monitored in term of demographics. The following information was recorded: gender, date of birth; diagnosis date, and survival at the final collection point. Decimal age was calculated from date of birth at every time point, by using the LMS Growth (Harlow Healthcare, UK) to allow growth comparison to the expected frequencies for the UK population (Cole, Freeman and Preece 1995).

4.2.3 Clinical information

Clinical information was collected from the medical notes. The type of tumour was classified using the international Classification of Childhood Cancer, Third Edition (ICCC-3) (Steliarova-Foucher et al. 2005) in order to assess the nutritional risks according to cancer type. Analysis of the data according to cancer stage was not possible due to the limited sample size.

Treatment protocols and treatment modalities were recoded in order to assess the nutritional risks according to treatments. However, due to the limited numbers available in the study and the wide range of treatment protocols used to treat childhood cancer, the cohort was grouped according to the wider treatment modalities of: chemotherapy only (with or without surgery); radiotherapy only (with or without surgery); chemotherapy and radiotherapy; surgery only; or no treatment. This information was recorded to allow data analysis in relation to cancer treatment.

The use of steroids was also recorded because of their effect on appetite and body composition. The use of steroids was classified depending on whether they were used as part of treatment protocol, as antiemetic, or to reduce intracranial pressure. This distinction was necessary because the dosage and length of treatment changes dramatically between intended purposes.

4.2.4 Anthropometric measurements

The patients were recruited after diagnosis as soon as advised it was appropriate to do so by the consultants. The first set of measurements was taken at the time of recruitment. Because of the time lapse between, diagnosis and actual recruitment, retrospective information for height and weight at diagnosis date was also collected

from the clinical notes. These provided essential information on growth pre-treatment.

The following measurements were collected every three months ± 4 weeks thereafter, up to a year. From a year after diagnosis, the measurements were taken every six months (± 3 months). This was to adjust to less frequent hospital attendance following the reduction in the intensity of treatments after the first year. The flexibility in the timing of follow up measurements was essential to accommodate the timing of the clinical practice.

4.2.4.1 Growth measurements

Height for children under the age of one and children unable to stand were measured using supine length on the supine measuring device SECA 399 (SECA Hamburg, Germany) available at clinics and in the ward. The child was measured with the help of a nurse or the child's parent using standard techniques. The parent was asked to hold the child's head with the eyes facing the ceiling, against the headboard. The researcher or nurse straightened the leg by placing a hand on both knees, keeping the toes pointing upwards and sliding the footplate up to the sole of the feet. Children over one year of age were measured using the wall-mounted stadiometer (SECA Hamburg, Germany) available in the ward and in clinic. The patient was measured without shoes and thick socks and he/she was positioned to touch the back plate with his/her back, heels and buttocks. The head was positioned to look straight ahead with the lower border of the bony orbit and the upper margin of the external opening of the auditory canal in the same horizontal line. The child was asked to breathe in while supporting the head in the right position and then asked to breathe out. The measuring board was placed on the top of the head and the height recorded. Height was measured to the nearest 0.1 cm.

Infants up to one year were weighed unclothed using a baby scale SECA 399 (SECA Hamburg, Germany). Children over one year of age were weighed without shoes on and with light clothing on the standing scales available in the ward or at clinic SECA 599 (SECA Hamburg, Germany). Weight was measured to the nearest 0.1 kg. Whenever it was not possible to measure height and weight of a child, the measurement was taken from the weight and height record file available in ward two

using the most recent recorded measurements. BMI was calculated as weight divided by height squared. In this study UK 1990 reference values were used to assess growth (Cole et al. 1995). At the end of 2010 new growth standards (RCPCH 2011; SACN/RCPCH 2007) for children aged 0-4 were introduced. However, they were not adopted in this study because they were published after the study was designed and at the final phase of data collection. Moreover, the use of the previous reference standards was believed to be more appropriate since clinical and nutritional judgment was based on the previous reference data (Cole et al. 1995). Height, weight and BMI centiles for children were calculated using LMS Growth (Harlow Healthcare, UK).

Height and weight before diagnosis were collected based on parents recall, to establish weight loss before diagnosis.

In this study BMI centiles were presented according to gender and diagnostic group (solid vs. haematological). Undernutrition was defined as BMI $\leq 2.3^{th}$ centile (SACN 2012). The prevalence of undernutrition observed in this study was compared to the expected frequencies of 2% for undernutrition for all children, 1.9% for boys and 2.1 % for girls (Scottish Government 2009).

In this study, overweight and obesity were defined using the threshold for population monitoring, as it is standard UK government practice (Department of Health 2012). Overweight was defined as $\geq 85^{th}$ / $< 95^{th}$ centile and obesity as $\geq 95^{th}$ centile (Cole et al. 1995). These definitions are widely used in UK (Department of Health 2012; Scottish Government 2009) therefore it was decided to use this definition to maintain consistency and to allow comparison with the published literature. The prevalence of overweight and obesity was compared against the most recent Nutrition and Diet National Survey (Department of Health 2012) result of 15% for overweight, and for obesity, 18% for boys and 19% for girls. The NDNS (Department of Health 2012) was chosen over the Scottish Health Survey (SHS) (Scottish Government 2009) because SHS 2008 provides data on Scottish children but does not distinguish between overweight and obesity, and the former is the most up to date survey.

4.2.5 Weight loss

Since a weight loss ≥ 5% in a month is a sign of nutritional deprivation (Jeejeebhoy and Keith 2005), in this study weight loss from the preceding measurement was assessed. This was expressed as a percentage of actual body weight. The prevalence of patients with a weight loss ≥5% was reported. Data were presented according to gender and diagnostic group.

4.2.6 Arm anthropometry measurements

The triceps skinfold (TSF) and mid upper arm circumference measurements were taken by the same investigator using standard technique as described in Chapter 3.2.2 (page 101). The full set of measurements was taken three times, and the mean of the three measurements was used for the analysis of data. Whenever only two or one measurement were available the mean of the two measurements or the single measurement was used for the analysis of data.

The raw data were compared to arm anthropometry reference values adjusted for age and gender. There are two sets of reference value for arm anthropometry available in the literature (Frisancho 1981; World Health Organisation 2011). In the current study, the Frisancho (1981) reference values were used. The decision was made because WHO (2011) reference values are only available for children up to five years of age and are therefore not suitable for this study. Moreover, the WHO (2011) data are based on figures from many countries over the world, whereas the Frisancho's (Frisancho 1981) are based on US children, which was believed to be more similar to the population in this study. Furthermore, the Frisancho reference values are those used at the RHSC by clinicians and dietitians. However, since the Frisancho (1981) reference values do not include children less than one year of age, the WHO reference values (World Health Organisation 2011) were used for those patients.

Since arm anthropometry parameters depend on growth, they could not be analysed as raw values and they were converted to centiles. However, Frisancho (1981) , only provides cut off points and not specific centile values ($\leq 5^{th}$ centile; 6-10^{th} centile; 10-25^{th} centile; 26-50^{th} centile; 51-75^{th} centile; 76-90^{th} centile; 91-95^{th} centile; $\geq 95^{th}$ centile). Therefore, to allow comparisons between genders and diagnostic group, arm

anthropometry measurements were also normalised for age and gender by expressing the as percentage of standard (50^{th} centile) (Frisancho 1981).

The crude measures of TSF (mm) and MUAC (mm) were used to calculate muscle , fat mass area and FM% using the following equation (Frisancho 1981).

$$A\ (mm^2) = \pi/4 * d^2$$

$$M\ (mm^2) = (C-\pi T)^2/4\pi$$

$$FM\% = F \times A/100$$

Where:

T= Triceps skin fold; A= Upper arm area; M= upper arm muscle area; F= upper arm fat area

d= MUAC/π.

Undernutrition was classified as TSF and MUAC $\leq 5^{th}$ centile (Frisancho 1981; Garofolo et al. 2005; Oguz et al. 1999; Smith et al. 1991). The cut off points to define obesity and overweight by arm anthropometry measurement are $\geq 85^{th}$ centile and $\geq 95^{th}$ centile respectively (Must et al. 1991). However, since Fisancho (1981) provides different cut off points, in the current study overweight and obesity were classified as $\geq$91-<95^{th} centile and $\geq 95^{th}$ centile respectively. The prevalence of malnutrition according to TSF and MUAC was presented according to gender and diagnostic group.

4.2.7 Bioelectrical Impedance Analysis

Bioelectrical impedance analysis was performed with an SF-BIA Quantum II RJL System at a single frequency of 50 KHz. The electrodes were placed following the manufacturer instructions. The instrument was calibrated at the beginning of the study and then monthly as per manufacturer instructions. The two upper electrodes were placed on the right hand skin covering the third metacarpal bone and the wrist, between the protruding portion of the ulnar and radial bone. The two lower electrodes were placed on the skin of the right foot covering the third metatarsal bone and the ankle on the level of protruding parts of the tibial and fibular bone. The patient was supine, with arms at 45° from the body in a position to guarantee that the

current would not pass through the bed. Those patients who were able to urinate were asked to do so before the measurements were taken. For those patients wearing nappies, the parent or the guardian where asked to remove the nappy before the BIA measurement. For the estimation of FM and FFM the only equation validated for the use in paediatric oncology was used (Brennan 1998).

Total body water (TBW) and FM were calculated using the following equations;

$$TBW = 1.24 + 0.56\ (HT^2/I)\ \text{(Brennan 1998)}$$

Where: HT= height; I= impedance.

FM and fat mass % were calculated to allow comparison to standard values. They were calculated using the following formula;

$$FM = BW - TBW$$

$$FFM\% = FFM \times BW/100$$

Where BW=body weight;

FM% was compared to reference values matched for age and gender. Because of the lack of a reference value covering the entire age range of this study, two separate reference values were used for comparison. For children from birth to five years of age, the Fomon et al. reference (Fomon et al. 1982) was used, whereas for the age range five to 18 years the Laurson et al. (2011) reference value was used. For the age range where both reference values were available the Laurson et al. (2011) was used, due to the bigger sample size used to establish the reverence values. Laurson et al. (2011) provide reference values according to centiles. For this study, the population group was compared to the 50^{th} centile. FM% was presented according to gender and diagnostic group.

4.2.8 Physical activity

Each patient who entered the study was asked to wear an accelerometer (Actigraph GT1M) for seven days at diagnosis, six months 12 months and 18 months. The Actigraph was worn around the waist above the iliac crest. Patients were offered the option to wear it using an elastic belt or using tegaderm^{TM} pads. The Actigraph was initialised for each patient using the manufacturer's software. The patients were

asked to wear the device during waking hours and to take it off when bathing, showering, during water sports and at bed time. Furthermore, they were asked to record in a diary provided to them the times when they wore the Actigraph and the time they went swimming or cycling. The Actigraph was returned by post (pre-paid envelope) or in person and then analysed using the manufacturer's software.

The Actigraph measures vertical accelerations and converts them to a number (counts) which is in turn summed over a period of time (15 seconds). The sedentary time was defined using total durations of counts below 50 counts/min^{-1} and in increments of 50 counts/min^{-1} up to 850 counts/min^{-1} (Ridgers ND et al. 2012). PA was presented according to gender and diagnostic group.

4.2.9 Dietary intake and nutrition support

Information regarding referral to a dietitian, and the reasons and the need for NS intervention (type and dosage) were recorded during the period of data acquisition. NS intervention was categorised as; use of oral calorie supplements (OCS); and/or enteral tube feeding (ETF) including nasogastric tube (NGT) gastrostomy tube (GT) or jejunal tube (JT); and/or parenteral nutrition (PN). 'Advanced NS' was defined as the need for ETF and/or PN. OCS was prescribed by the specialist paediatric oncology dietitians. ETF and PN were used after discussion between the oncology multidisciplinary team and the hospital NS team (NST). The need for NS was presented according to diagnostic group and treatment modalities.

The dietary intake for macronutrients was assessed at each time point. Dietary intake was assessed both *ad libitum* and with NS. This was essential to assess the energy and macronutrients contributed by the NS towards meeting the energy and dietary requirements. The type and dosage of NS were used to calculate nutrient intake with NS by adding the energy and micronutrients coming from the nutrition support to those coming from the intake *ad libitum*.

Initially, the dietary assessment method of choice to assess dietary intake *ad libitum* was the three day diet diary. However, from the beginning, it became evident, that the parents were under too much pressure to be able to complete the diary. Therefore it was decided to use the 24 h multiple pass diet recall instead. In the current study the protocol developed by the United States Department of Agriculture for use in its

food survey was used (Guenther et al. 1994). This method is less of a burden for the family hence it was believed to increase compliance. Even though it is subject to some error at individual level (Johnson et al. 1996), it still provided useful information on energy macronutrients intake.

The patient or guardian was asked if the previous 24 h were a typical day of the previous two weeks diet. If so they were ask to recall all the food and beverage consumed in the previous 24 h. In the case that the previous 24 hours were not representative of the patients' last two weeks intake, the guardian or parents were asked to recall all the food and beverage consumed in 24 h of a representative day. In cases where the previous two weeks intake was heterogeneous the guardian or parents was asked to recall all the food and beverage consumed in 24 h for an example of both good days and bad days proportionally, so the intake could be averaged accordingly.

The parent was asked to provide a list of food and beverages the child consumed the day before from midnight to midnight. After the first listing of food, the parent was asked questions on the time the food and beverages were consumed and the name of the eating occasion (e.g. breakfast, mid morning snack etc.). The parent was then asked to review the previous day's dietary intake again. This time details of portion sizes, brand names and preparation methods were recorded. The patient/parent/guardian was asked to remember if any food was left on the plate, and to describe the food as clearly as possible with attention to combination dishes. The estimation of food portion size was done using description of portion sizes. The patient/parent/guardian was also asked to provide packaging of pre-packaged food where available.

Once the 24 h multi pass recall was completed, the investigator asked about food groups such as meat, fish, dairy, vegetables, fruit, sweets, chocolate, and beverages, to countercheck if any food was forgotten. Finally, the list was read back to the participant to check further if the recall was correct or if they forgot to mention any food that was consumed.

The information gained from 24 h diet recall was then analysed using the computer programme WINDIETS (Univation Ltd 2005) to calculate daily intake of macronutrients. Due to the limitation of the 24 h diet recall on estimating micronutrients intake only estimates of energy (kcal) protein (g) fat (g) and carbohydrates (g) were obtained. When the composition of a food consumed by a patient was not available on WIN diet, the manufacturer's information was used. The composition of NS was obtained from the manufacturer and used to calculate nutrient intake in relation to the quantity consumed.

In the time period the research took place, new energy reference values for the UK population were published by the Scientific Advisory Committee on Nutrition (SACN 2011) which replacing the Estimate Energy Requirements (EARs) from the Department of Health (1991). The EARs from the Department of Health (1991) are based on TEE derived by the Schofield prediction equation (Schofield et al. 1985) which also formed the basis for the document *Energy and protein requirement* (FAO/WHO/UNU 1985). Schofield et al. (1985) reviewed 114 published papers on basal metabolic rate (BMR) totalling 7173 data points to produce a predictive equation for BMR. However, this study had the major limitation of containing a disproportionate number of Italian subjects (47%) and relatively few subjects from the tropical region. This equation has been reported to overestimate BMR and its use in the present day with an increase prevalence of obesity has been questioned (SACN 2011). For this reason a new equation (Henry 2005) was developed using a data set which included a much larger number from the tropics compared to the Schofield et al. (1985) and excluded all Italian subjects. This new equation was adopted by the SACN (2011) to establish the new EARs for energy and has been recently embraced in dietetic clinical practice

Therefore, to assess whether the patients were meeting their energy requirements, the energy intake of the study population both *ad libitum* and with NS were compared to total daily energy expenditure calculated for each patient using the Henry (2005) prediction equation matched for age and gender. Considering the health condition and the reduced physical activity of this study cohort in response to the disease and treatments, (Aznar et al. 2006; Jacob et al. 2007; Jansen et al. 2009; Sanford et al.

2008), the daily rate of total energy expenditure for both equations was calculated by multiplying the basal metabolic rate by the activity level factor for less active children (FAO 2004) as shown in Table 4.1.

In the dietetic management of adults cancer patients a stress factor is added to BMR to account for the metabolic demand of cancer (Barak et al. 2002; Delarue et al. 1990). However, the energy requirements in children are estimated without accounting for the metabolic demand of cancer. This is because, the is no evidence for increased REE during cancer therapy in children (den Broeder et al. 2001; Schmid et al. 2005; Stallings et al. 1989; Vaisman et al. 1993). The literature lacks information regarding stress factors specific for pediatric cancers, and those available for adults are believed to be to high: i.e. 25-34% (leukaemia)(Barak et al. 2002) and 0-20% (lymphoma)(Barak et al. 2002; Delarue et al. 1990), especially considering the increased risk of late onset of obesity in this patient group. Therefore, in the current study, the estimated energy requirement was calculated based on the Henry equation (Henry 2005) adjusted for age, gender and physical activity, without adding a stress factor.

Table 4.1 Physical activity level (PAL) values for use in calculation of EARs of children and adolescents with low physical activity adjusted for growth (FAO 2004)

Age group (years)	**PAL 25th centile for less active children**
1-<3	1.36
3<10	1.43
10-18	1.68

Adequacy of intake for protein, fat and carbohydrates was assessed by comparing intakes to the reference values for healthy subjects matched for age and gender (Department of Health 1991; Department of Health Report on Health and Social Subjects 1994).

Date of beginning and end of NS, and BMI centile at initiation and end of nutrition support were recorded in order to assess the effectiveness of nutrition support on improving nutritional status and/or preventing further nutritional deterioration. Vitamin supplements (dose, type and brand name when available) were recorded to allow interpretation of plasma vitamins.

4.2.10 Blood parameters

Blood was taken by NHS staff, ideally on the same day as the other measurements. However, for ethical reasons blood could only be collected when the patient's veins were accessed for routine blood test or therapy. If it was not possible to collect the blood the same day as the measurements, the blood was collected at the closest time possible, dictated by clinical practice. All blood was analysed by the RHSC Edinburgh Lab, apart from the vitamins and minerals which were analysed using standard techniques by the RHSC in Glasgow. The results were compared with the NHS RHSC Edinburgh Lab reference values.

Nutritional status of Vitamin A, D (25-Hydroxycholecalciferol) Vitamin E/Cholesterol Selenium, Zn, Cu, folate, Vitamin B12 was assessed by measuring plasma levels. Because of the effect of low plasma 25 (OH) D on PTH secretion and bone turnover, plasma PTH was also measured.

Since the liver has a pivotal role in nutrient metabolism, liver function was assessed measuring bilirubin, alanine transaminase (ALT), albumin, g-glutamyl transferase (GGT) and alkaline phosphatase (ALP) at each time point.

Serum High Sensitivity C-reactive protein (hsCRP) was used as biochemical marker of inflammation. In order to assess whether, plasma changes in ferritin, Cu, Zn were caused by changes in nutritional status rather than inflammation, a cross sectional analysis was conducted.

Since the kidneys regulate fluid homeostasis, acid-base balance and renal function were assessed by measuring blood urea, creatinine and electrolytes (Na+, K+, Mg^{2+}, PO_4, HCO_3 & Ca^{2+}).

The study experimental protocol is shown in Figure 4.1

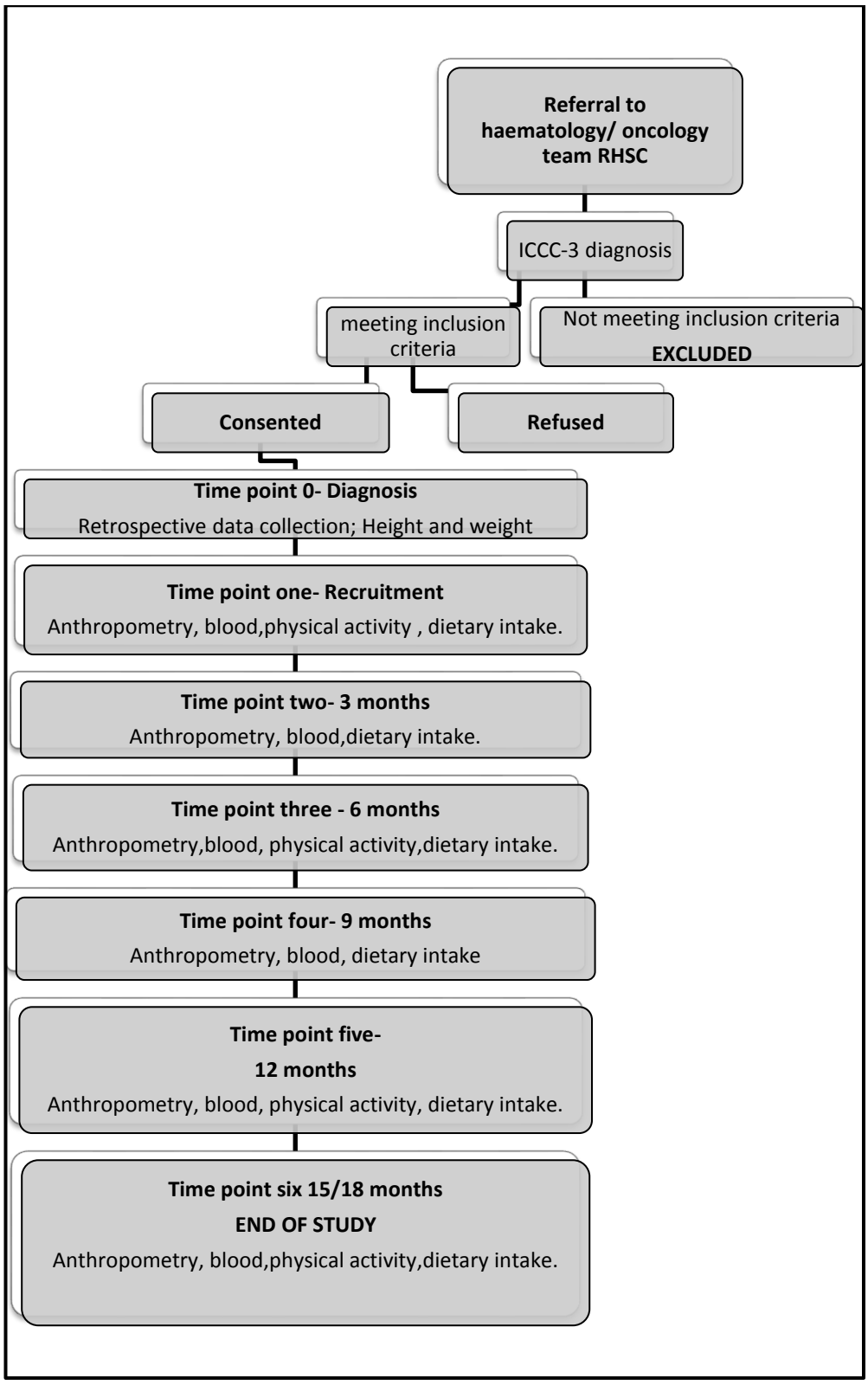


Figure 4.1 Schematic experimental protocol

4.2.11 Data analysis

Data were analysed using SPSS 19® (IBM®). The data were tested for normal distribution by the Shapiro-Wilk Test. The results are presented as mean (± SD) for normally distributed data and median (IQR) when not normally distributed.

For comparison according to gender (male vs. female) and diagnosis (solid vs. haematological) an Independent t- test was carried out. For comparison of the same group at two different time points a one sample t-test was carried out. The equality of variance was first tested by the Levene's test. If the test was not significant ($p>0.05$) equal variances were assumed.When the data where non-parametric comparison according to gender (male vs. female) and diagnosis (solid vs. haematological) was tested by the Mann-Whitney test. For comparison of the differences between before and after NS, the Wilcoxon signed-rank test was used.

Correlation between variables was tested using Pearson correlation for parametric data and Spearman's correlation for non-parametric data. Difference between observed and expected frequencies of undernutrition, overweight and obesity were tested for significance using the Z test.

The limit of agreement between anthropometric parameters for detecting undernutrition was identified by the Kappa test.The results were considered significant when $p<0.05$.

4.3 Results

4.3.1 Subjects

Sixty-four patients in total were referred to the oncology and haematology clinic between 1st August 2010 and 31st December 2011. Of those, 13 were not diagnosed with cancer and discharged from the service. The remaining 51 patients were diagnosed with malignant cancer and benign brain tumours and met the diagnostic inclusion criteria for the study. A flow diagram illustrating the composition of the cohort in terms of meeting the inclusion criteria and consent is shown in Figure 4.2

Ultimately, 35 patients were eligible and 26 connsented to take part to the study representing a 74% recruiment ratio. Of these patients, 18 were male (69%) and 8 (31%) were female ; the median age at diagnosis was 5.1 (inter-quartile range (IQR)

2.3, 7.9). The overall survival rate at the end of the study period 31/1/2012 was 91%. Table 4.2 indicates the primary cancer diagnosis percentage within the whole cohort, and the associated survival rate at the end of monitoring period.

Due to the limited numbers available in the study, it was not possible to carry out data analysis according to primary cancer diagnosis. Hence the cohort was grouped according the wider definition of solid and haematological cancer. Of the total cohort 16 patients (62%) had solid tumours (including benign brain tumours) and ten (38%) had haematological cancer.

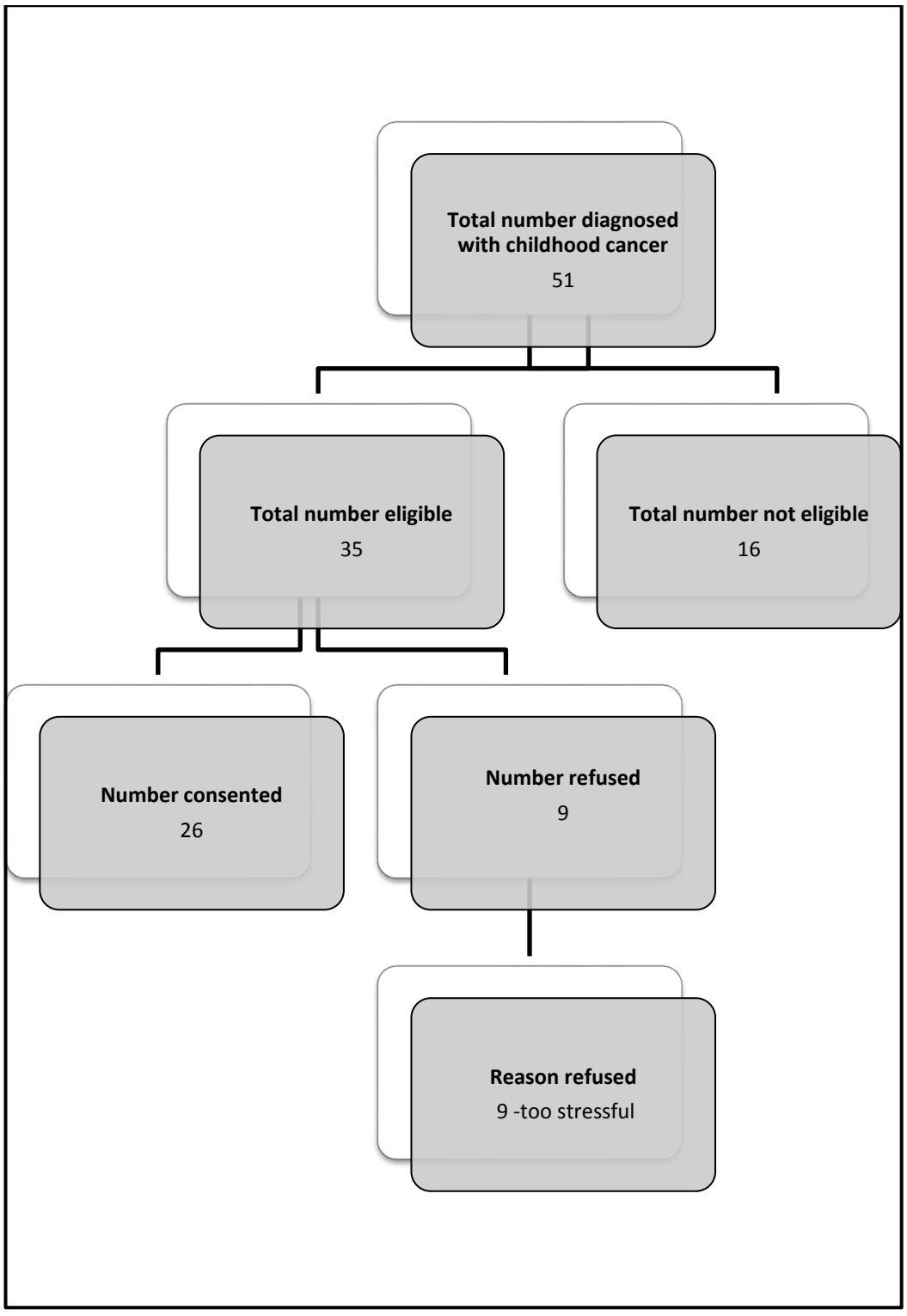


Figure 4.2 Patient accrual flow diagram of the patients referred to the RHSC with a cancer and benign brain tumour diagnosis

Table 4.2 Primary cancer diagnosis percentage within the cohort and survival rate at end of monitoring period on 31/1/2012

Diagnosis	Cases (% within cohort)	Survivors (% with diagnosis)
I - Leukemia	**10 (38)**	**10 (100)**
ALL	**8 (31)**	**8 (100)**
AML	**2 (7)**	**2 (100)**
CML	**0**	**-**
Solid tumours	**13 (50)**	**12 (88)**
II- Lymphoma	**2 (8)**	**2 (100)**
III -CNS tumour	**1 (4)**	**0 (-)**
IV- Neuroblastoma	**3 (11)**	**3 (100)**
V- Retinoblastoma	**1 (4)**	**1 (100)**
VI -Renal tumour	**2 (8)**	**2 (100)**
VII -Hepatic tumour	**0 (-)**	**-**
VIII -Malignant bone tumours	**0 (-)**	**-**
IX- Soft tissue sarcoma	**3 (11)**	**3 (100)**
X -GCT	**1 (4)**	**1 (100)**
XI- Malignant epithelial neoplasm	**0 (-)**	**-**
XII- Others and unspecified malignat neoplasms	**0 (-)**	**-**
III-Benign brain tumour	**3 (11)**	**3 (100)**

Due to the limited numbers available in the study and the wide range of treatment protocols used to treat childhood cancer, the cohort was grouped according the wider

classification of the treatment modalities received as described in the section 4.2.3. Table 4.3 shows the distribution of the treatment modality as percentage of the entire cohort measured.

Table 4.3 Treatment modality

Treatment modality	**Cases (% within cohort)**
Chemotherapy alone	15 (58)
Chemotherapy with surgery	4 (15)
Chemotherapy with surgery and radiotherapy	6 (23)
Surgery alone	1 (4)
Radiotherapy alone	0 (-)

Because of their effect on appetite and body composition, the use of steroids was recorded. Since steroid treatments are very complex to report as dose and length of treatment , they were classified as shown in Table 4.4 (i.e. use as per protocol)

Table 4.4 The use of steroids during data collection and reasons.

Reasons	**Recruitment n= 26**	**3 months n= 20**	**6 months n= 13**	**9 months n= 10**	**12 months n= 7**	**15/18 months n= 2**
As per protocol	10	9	5	4	3	2
Antiemetic	4	2	0	0	0	0
No steroids	10	0	7	6	4	0

4.3.2 Assessment of nutritional status using body mass index (BMI) , arm anthropometry and bioelectrical impedance measurements

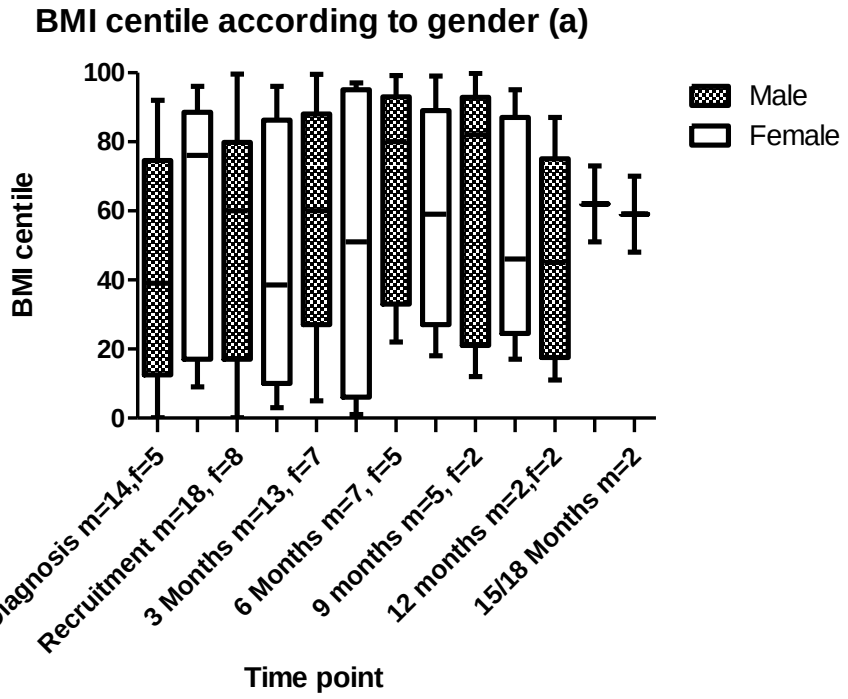
Nutritional status was assessed at each measurement by several anthropometric parameters (weight, BMI, weight loss, TSF and MUAC).

4.3.2.1 Body mass index (BMI) measurements

The prevalence of undernutrition and overnutrition was investigated at each time point according to gender and cancer type. With only 26 patients and 13 diagnostic categories assessment of the nutritional status according to diagnosis was not possible. Therefore the cohort was divided in two subgroups: solid and haematological malignancies. Figure 4.3 shows median (IQR) according to gender (a) and diagnosis (b) at each time point.

Median BMI centiles were within normal ranges for both genders and type of cancer during the entire data collection period. For the entire sample of males, the lowest BMI centile was found at diagnosis (median 39.9, IQR 16.2-69.5) whereas for the entire sample of females, the lowest median BMI centile was observed at recruitment (median 38.5, IQR 10.0-86.2).

When analysed according to diagnostic group, it emerged that for the entire sample of haematological patients, the lowest mean BMI centile was found at 12 months (median 24, IQR 17.5-55.5), whereas for the entire sample of solid cancer patients, the lowest median BMI centile was observed at recruitment (median 18.0, IQR 7.5-54.2). Interestingly, there was not a significant difference in nutritional status between the male and the female group measured by BMI centiles at any measurement ($p<0.05$ for all). On the other hand, BMI centile was significantly higher in the haematological group compared to the solid group at recruitment and at three months ($p<0.05$ for all).



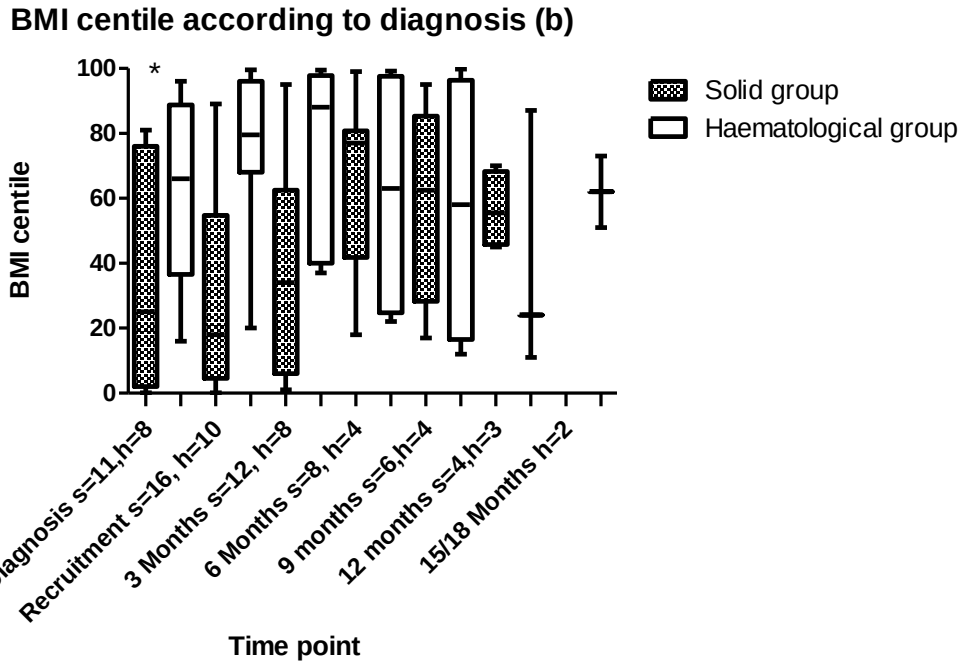


Figure 4.3 BMI centile according to gender (a) and diagnosis (b)* p<0.05 haematological vs. solid

Because of the small sample size, the prospective nature of the study, and the many drop outs due to patients deceasing or becoming palliative during the data collection period, it was not possible to carry out a general linear model for repeated measurements to assess BMI changes over time.

The highest prevalence of undernutrition according to BMI centile ≤ 2.3th centile (Figure 4.4) was observed at diagnosis and recruitment (21%, n = 3; 12 %, n= 2 respectively) for the male group, and at three months for the female group (14%, n = 1).

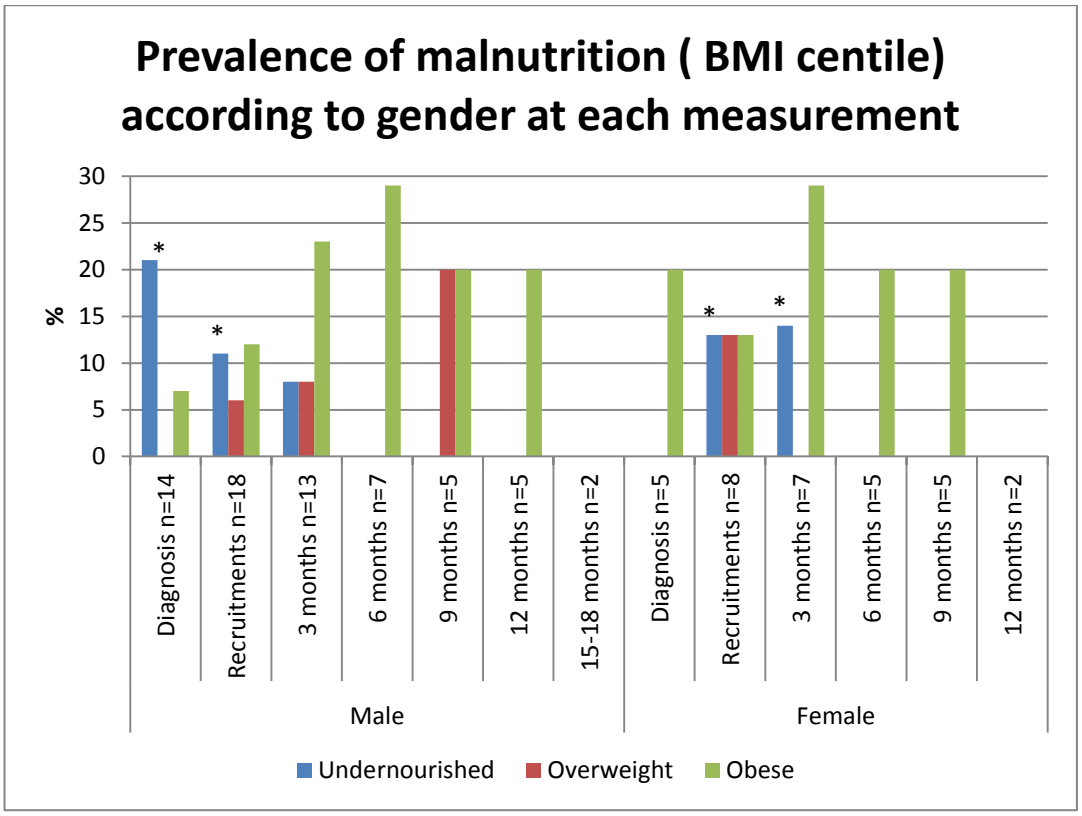


Figure 4.4 Prevalence of malnutrition according to gender at each measurement expressed as percentage (%). Undernutrition (BMI ≤2.3th centile), obesity (BMI ≥ 95th centile), overweight (BMI ≥ 85th/< 95th centile).* p<0.05 vs. UK prevalence (Department of Health 2012)

The observed frequencies of undernutrition and overnutrition were compared to the expected frequencies for the UK population (Department of Health 2012) according to gender. There was a significant increase in the prevalence of undernutrition measured as BMI ≤2.3th centile in the male group at diagnosis (p<0.05; 95%

CI -0.9% to 40.9%) and recruitment (p<0.05; 95% CI -3.0% to 27.4%) and in the female group at recruitment (p<0.05; 95% CI -10.2% to 36.5%) and three months (p<0.05; 95% CI -11.7% to 39.7%). The prevalence of overweight and obesity did not differ from the expected frequency at any measurements in either group.

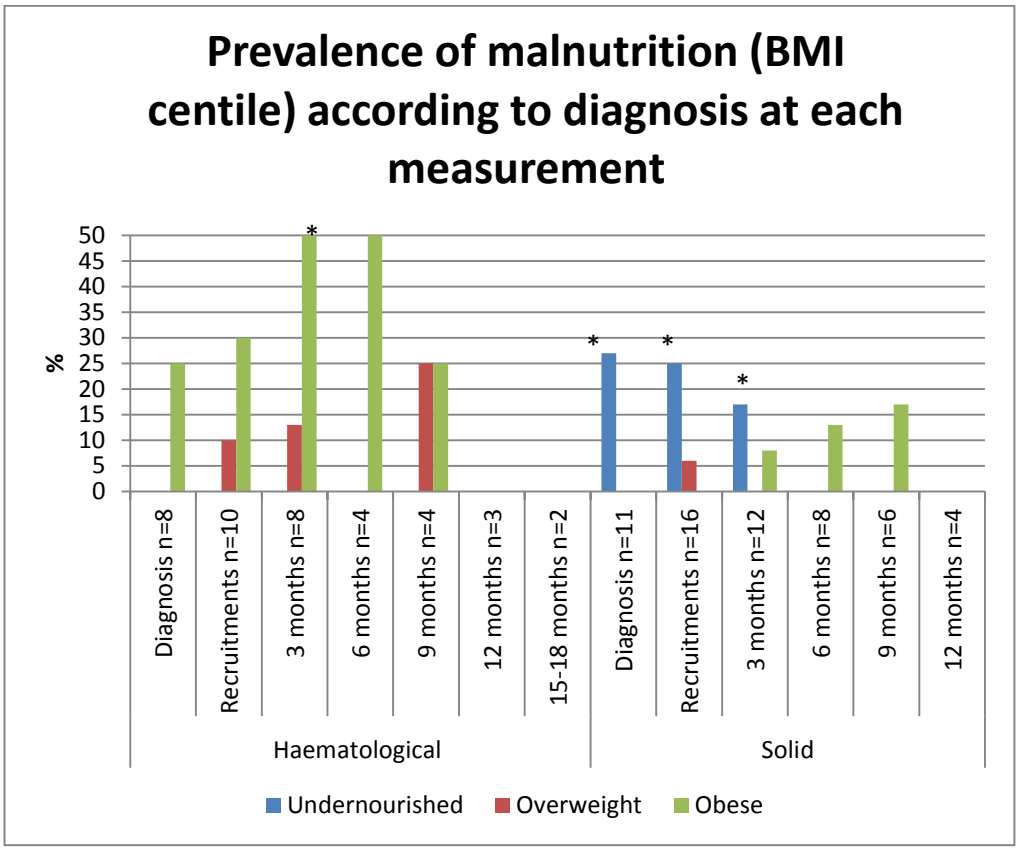


Figure 4.5 Prevalence of malnutrition according to diagnostic group at each measurement expressed as percentage (%). Undernutrition (BMI≤2.3th centile), overweight (BMI ≥ 85th / < 95th centile).* p<0.05 vs. UK prevalence (Department of Health 2012)

When the data were analysed according to diagnostic group (Figure 4.5), the highest observed frequency of undernourished children with BMI centile ≤2.3th was among the solid tumour group. In this group, 27 % (n = 3), 25% (n = 4) and 17% (n = 2) of patients were undernourished at diagnosis, recruitment and three months respectively, compared to 0% at every time point for haematological cancers. The highest observed frequency of obesity occurred in the haematological group at both three months (50%, n = 4) and six months (50%, n = 2).

There was a significantly higher prevalence of undernutrition (measured as BMI ≤2.3th centile) in the solid tumour group at diagnosis (95% CI 0.7% to 53.2 %), recruitment (3.8% to 46.2%) and three months (-4.2% to 38.2 %; $p<0.05$ for all). However, the prevalence of undernutrition did not differ from the expected frequencies for the UK population ($p>0.05$) for the group with haematological tumours. The observed frequency of children with a BMI centile above 95 was statistically higher than the expected frequency of 18% (Department of Health 2012) for the haematologic group at three months ($p<0.05$; 95% CI 19% to 80.6%). The observed frequency of overweight for both diagnostic groups was not significally different from the expected frequency ($p>0.05$ for all).

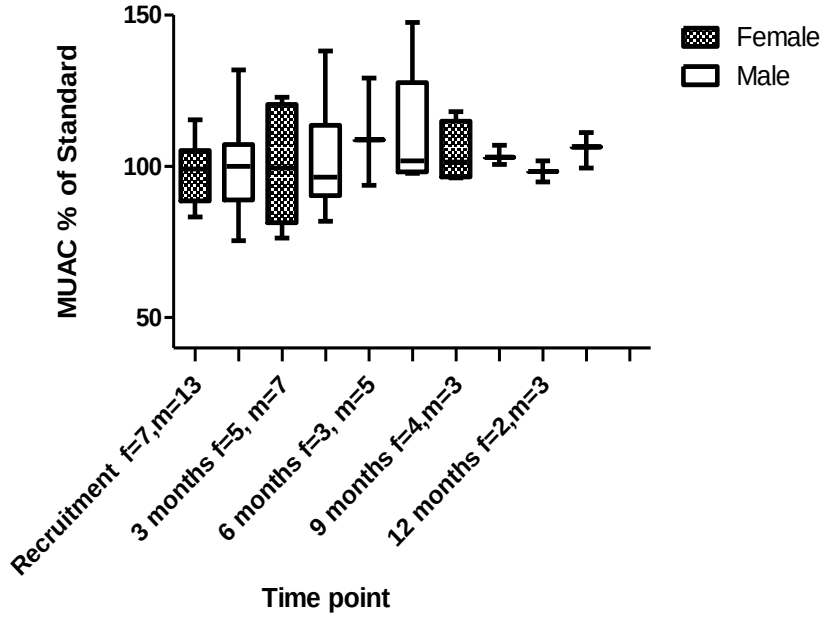
4.3.2.2 Weight loss over 5% from previous measurement

Weight loss ≥5% from previous measurement, was observed in three different patients at both recruitment (n= 2 solid tumour; n= 1 haematological cancers) and three months (n= 1 solid tumour; n =2 haematological cancers). Five out of six patients with a weight loss ≥5% were classified as normally nourished by all anthropometric measurements. All the patients apart from one with a solid tumour were started on NS.

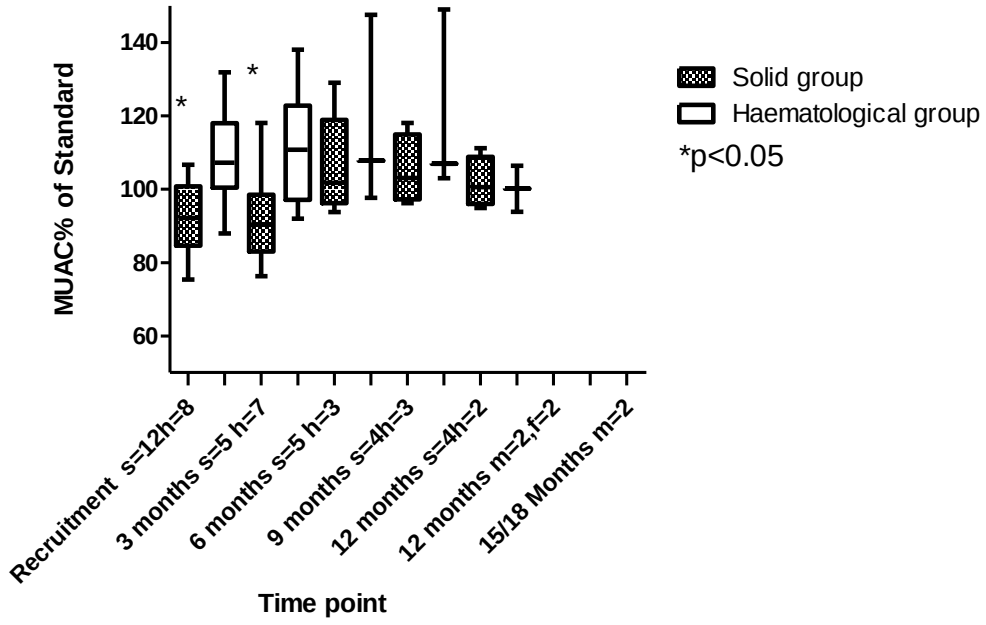
4.3.2.3 Arm anthropometry

In order to assess the prevalence of malnutrition at each time point, arm anthropometry measurements (MUAC and TSF) were converted to gender and age specific centiles (Frisancho 1981). However, the conversion of TSF and MUAC to centiles (Frisancho 1981) generates categorical data, hence calculation of centile mean and SD was not possible. Therefore, in order to normalise the data for age and gender and to allow statistical comparison between genders and diagnostic groups, the results where also expressed as percentage of standard value as described in the methodology section. Since only one patient had arm anthropometry measured at 15-18 months, the data for the last time point is not presented. Figure 4.6 shows arm anthropometry expressed as % of standard value at each time point according to gender and diagnosis.

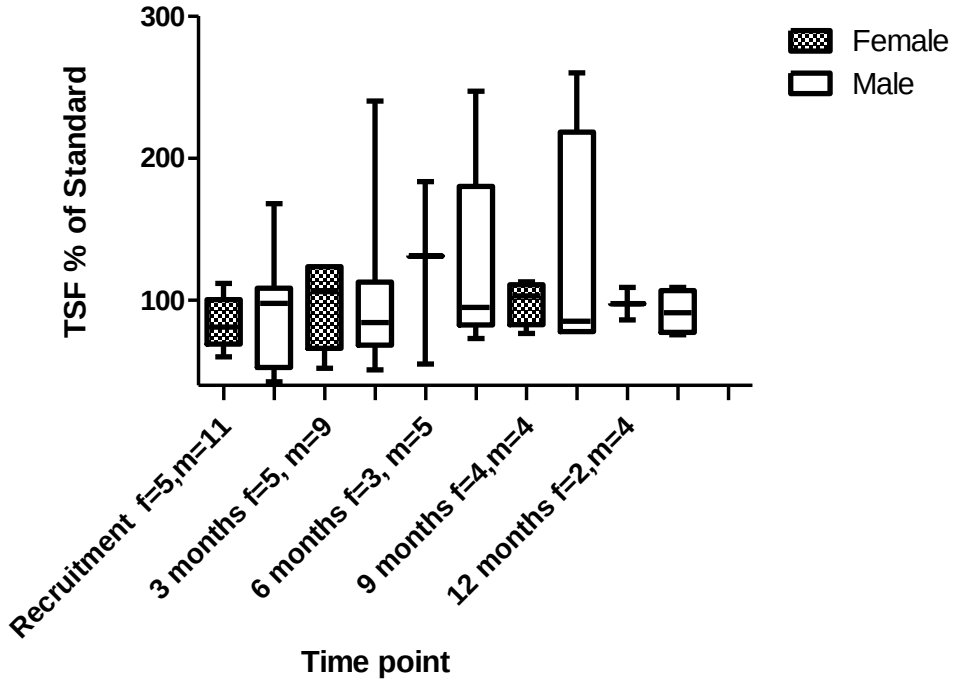
MUAC % of standard according to gender (a)



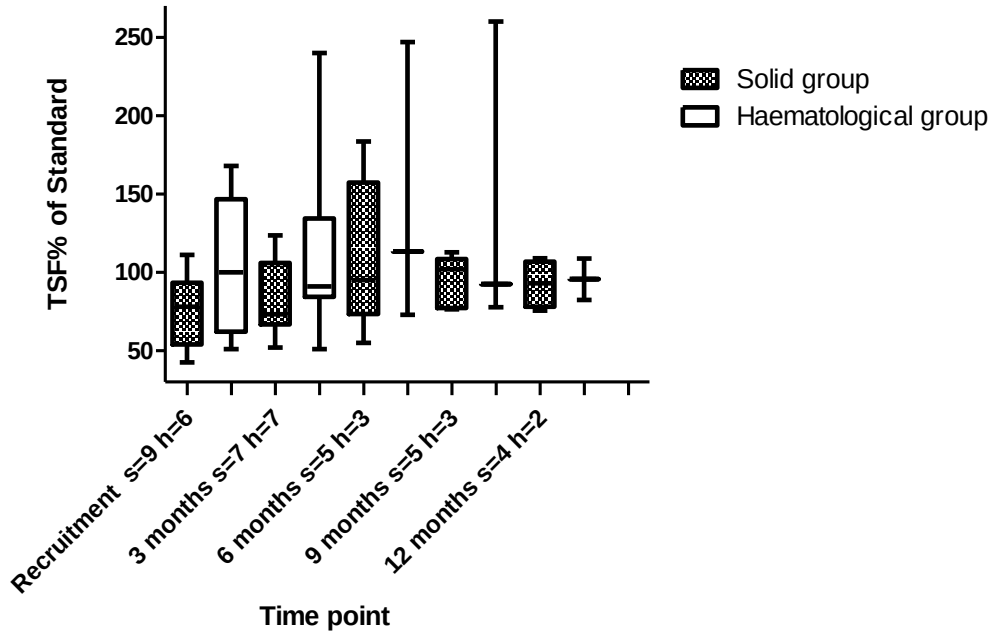
MUAC % of standard according to diagnosis (b)



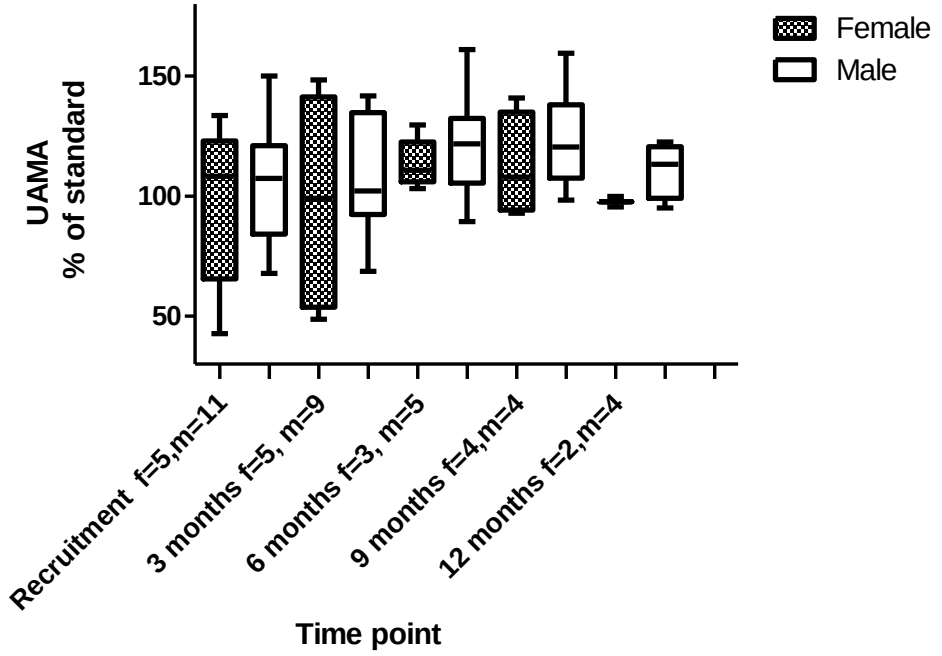
TSF % of standard according to gender (c)



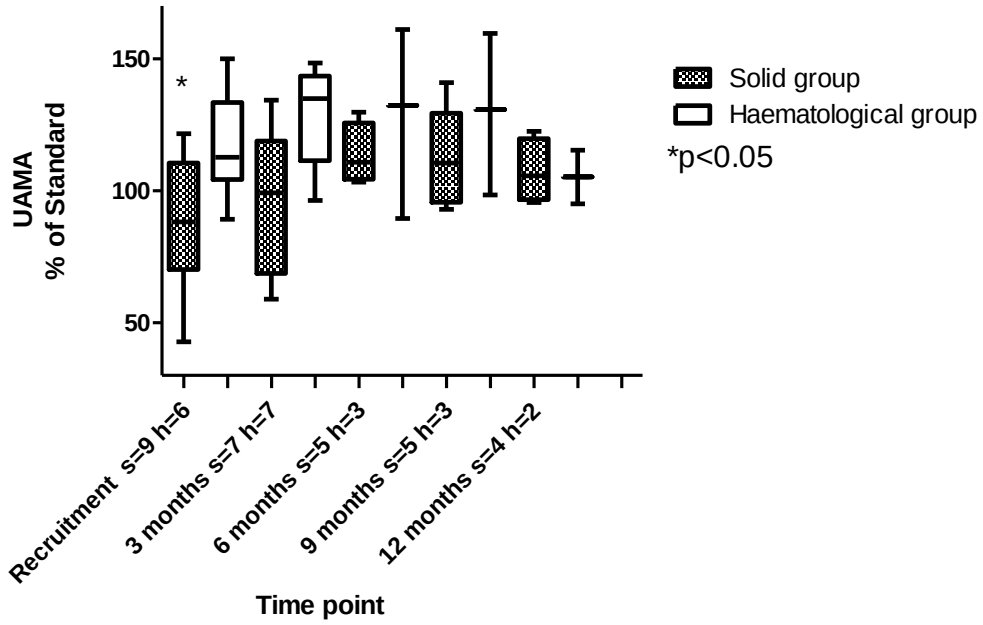
TSF % of standard according to diagnosis (d)



UAMA % of standard according to gender (e)



UAMA % of standard according to diagnosis (f)



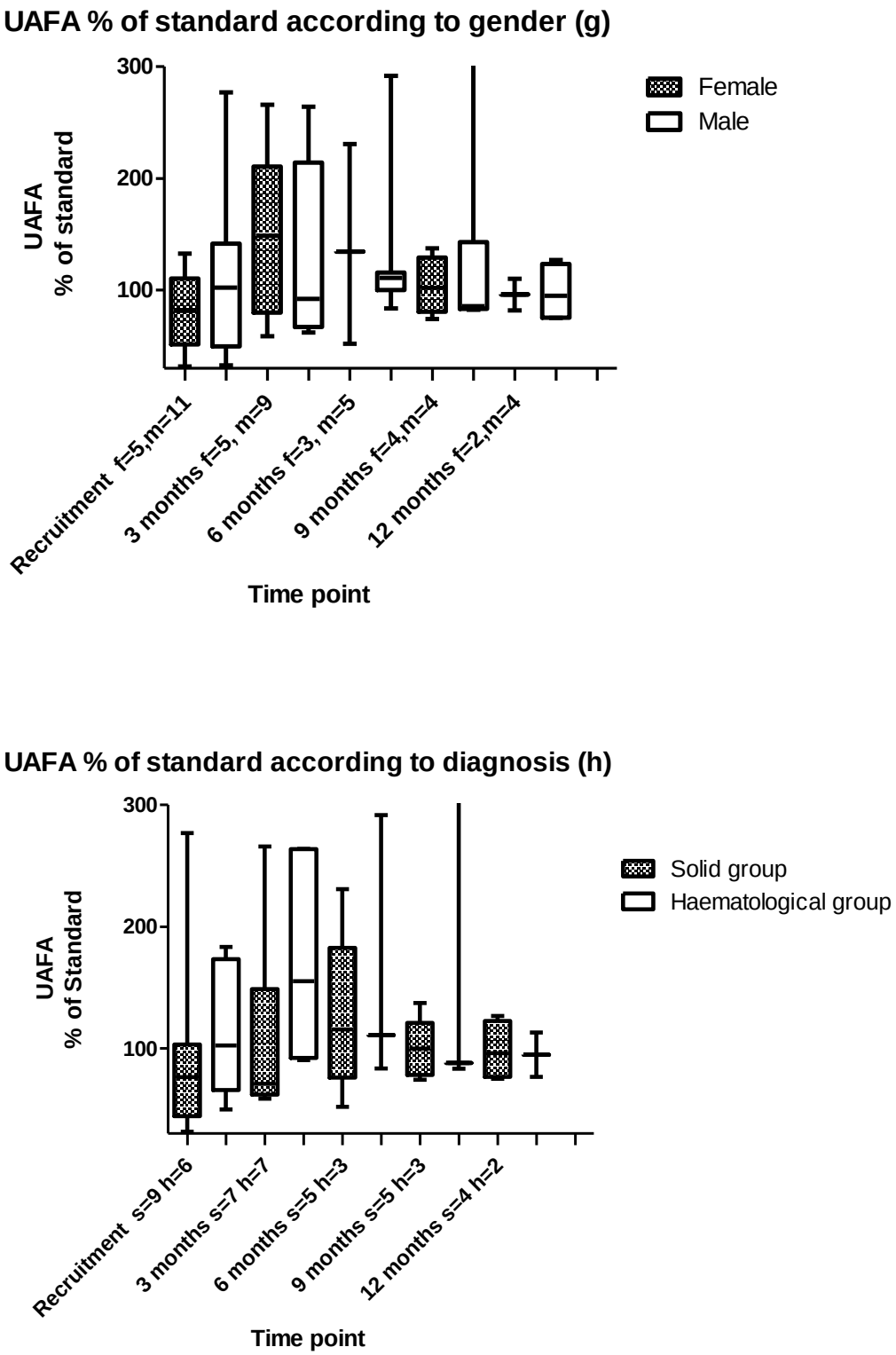


Figure 4.6 Arm anthropometry expressed as % of standard value.

Patients with solid tumours had lower TSF, MUAC, UAMA and UAFA than haematological patients for the first nine months of treatments. However, only MUAC at recruitment and three month, and UAMA at recruitment, reached statistical significance ($p<0.05$). Additionally, comparison of TSF, MUAC, UAMA and UAFA according to gender, showed no apparent differences between males and females.

In the solid group, the highest nutritional depletion was observed at three months, where TSF and UAFA were 73.3 % (IQR 68.3-93.0) and 70.8 %(IQR 62.6-124.8) of the standards, respectively. On the contrary, the haematlogical goup showed excess body fat accumulation at three months with the median UAFA being 129.4 % (IQR 96.5-202.6) of standard. In both groups, all arm anthropometry parameters returned to normal values by 12 months.

There was a positive association between BMI centile and UAFA centile measured by arm anthropometry at recruitment ($p<0.001$, $r= 0.743$) (Figure 4.7).

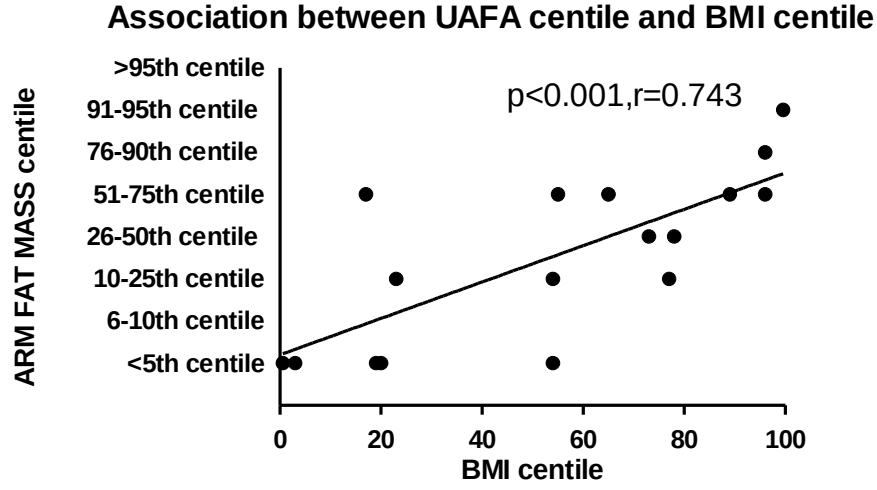


Figure 4.7 Spearman's correlation between arm fat mass centiles and BMI centile.

Due to the longitudinal design, the limited number of patients and the many drop outs, it was not possible to statistically analyse the changes in arm anthropometry over time either as raw data or centiles.

The prevalence of malnutrition at each time point was assessed using MUAC and TSF centiles. Undernutrition was classified as TSF and MUAC $\leq 5^{th}$ centile (Frisancho 1981; Garofolo et al. 2005; Oguz et al. 1999; Smith et al. 1991). Overweight was classified as ≥ 91-$< 95^{th}$ centile and obesity as $\geq 95^{th}$ centile (Frisancho 1981).

The prevalence of malnutrition assessed by MUAC is presented according to gender (Figure 4.8) and diagnosis (Figure 4.9) at each time point. For the male group the highest prevalence of undernutrition was observed at diagnosis (n= 5; 29%) whereas for the female group it was observed at three months (n= 2; 28%). The highest prevalence of obesity was observed at nine months in the male group (n= 4; 25%) and at six months (n= 1; 25%) in the female group.

For the solid cancer group the highest prevalence of undernutrition was observed at diagnosis (n= 6; 37.5%). From six months onwards none of the patients were classified as undernourished. Moreover, none of the patients with solid tumours were classified as overweight or obese during the entire data collection period.

For the haematological group, the highest prevalence of obesity was observed at six months (n= 3; 66%) and nine months (n= 2; 66%). None of the patients with haematological malignancies were classified as undernourished by arm anthropometry during the entire data collection period.

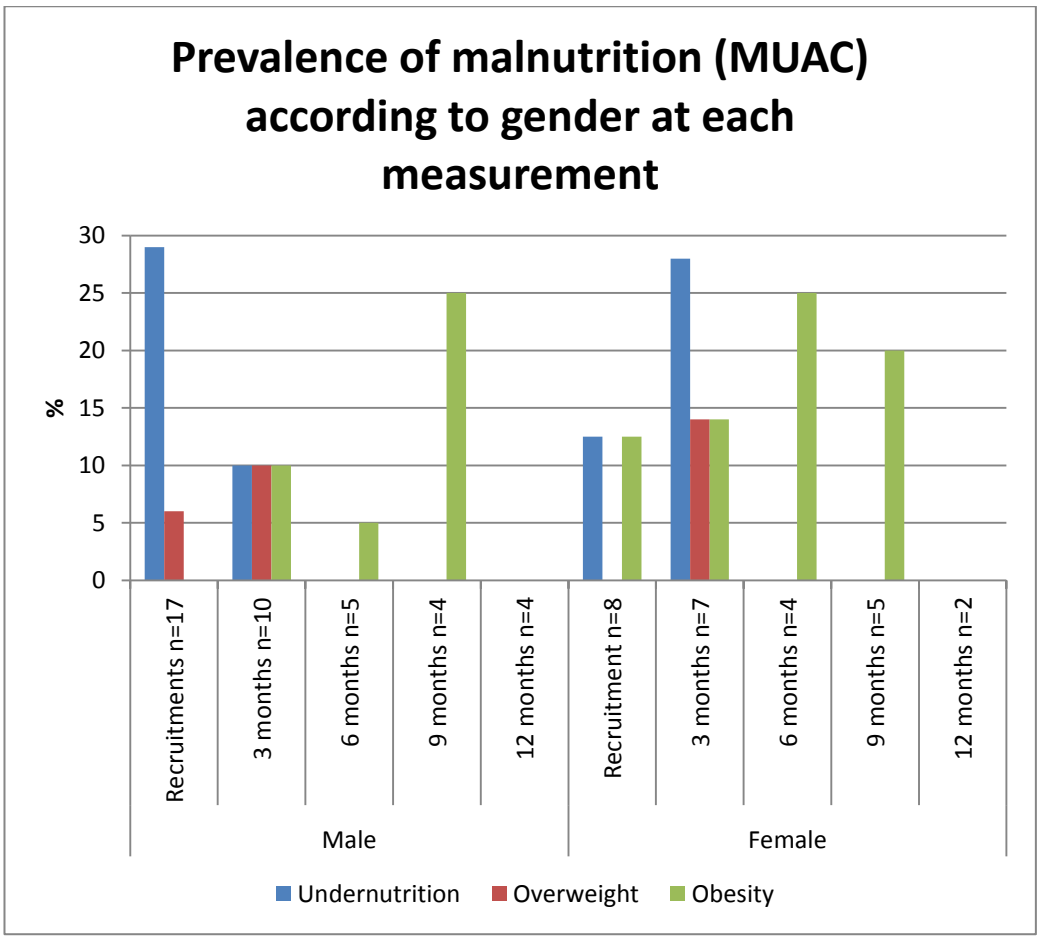


Figure 4.8 Prevalence of malnutrition according to gender at each measurement expressed as percentage (%). Undernutrition (MUAC≤5th centile), overweight (MUAC ≥ 91th/ <95th centile), obesity (MUAC≥ 95th centile).

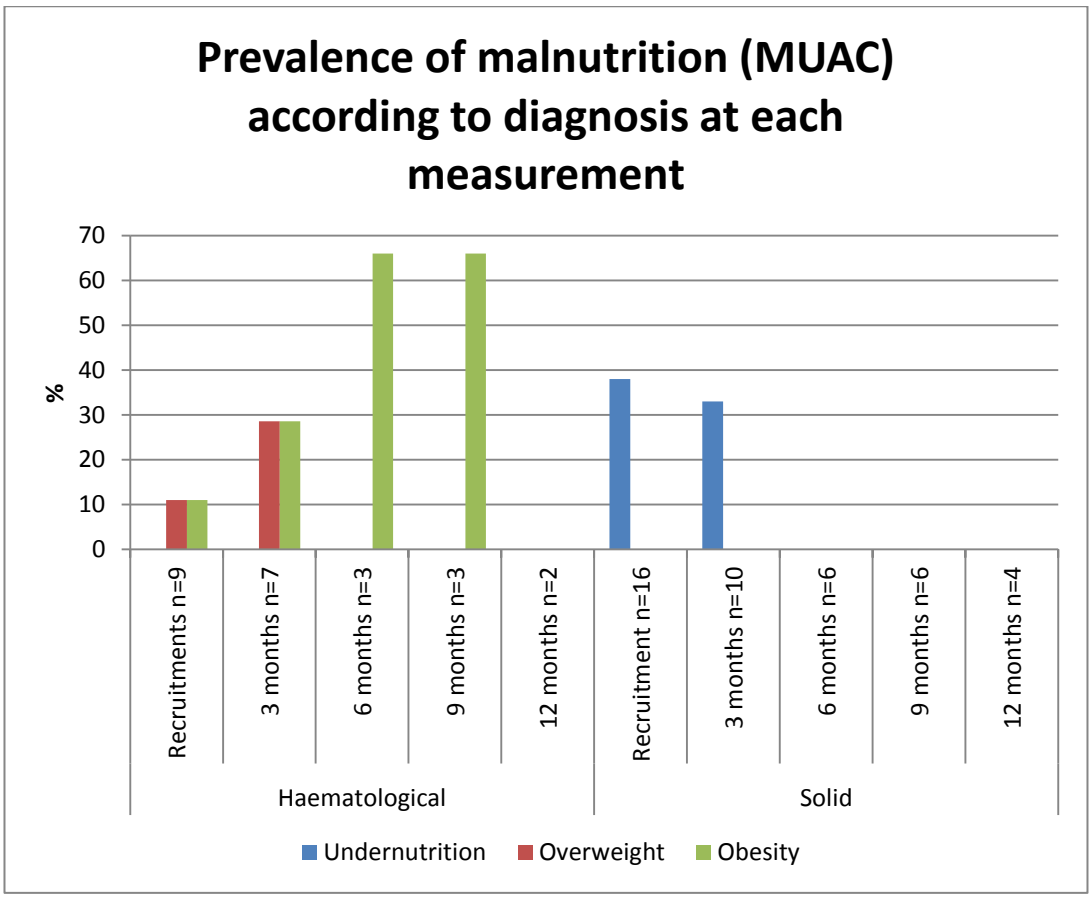


Figure 4.9 Prevalence of malnutrition according to diagnostic group at each measurement expressed as percentage (%). Undernutrition (MUAC≤5th centile), overweight (MUAC ≥ 91th/<95th centile), obesity (MUAC≥ 95th centile).

The prevalence of malnutrition assessed by TSF is presented according to gender (Figure 4.10) and diagnosis (Figure 4.9) at each time point. For the male group the highest prevalence of undernutrition was observed at diagnosis (n= 5; 36%) whereas for the female group it was observed at six months (n= 1; 25%). The highest prevalence of obesity was observed at six months in the male group (n= 1; 20%), and at six months (n= 1; 25%) and nine months (n= 1; 25%) in the female group.

For the solid cancer group the highest prevalence of undernutrition was observed at diagnosis (n= 6; 35%). From nine months onwards none of the solid cancer patients were classified as undernourished. For the haematological group, the highest prevalence of obesity was observed at six months (n= 2; 66%). No individual child with haematological cancer was undernourished for the entire collecting period

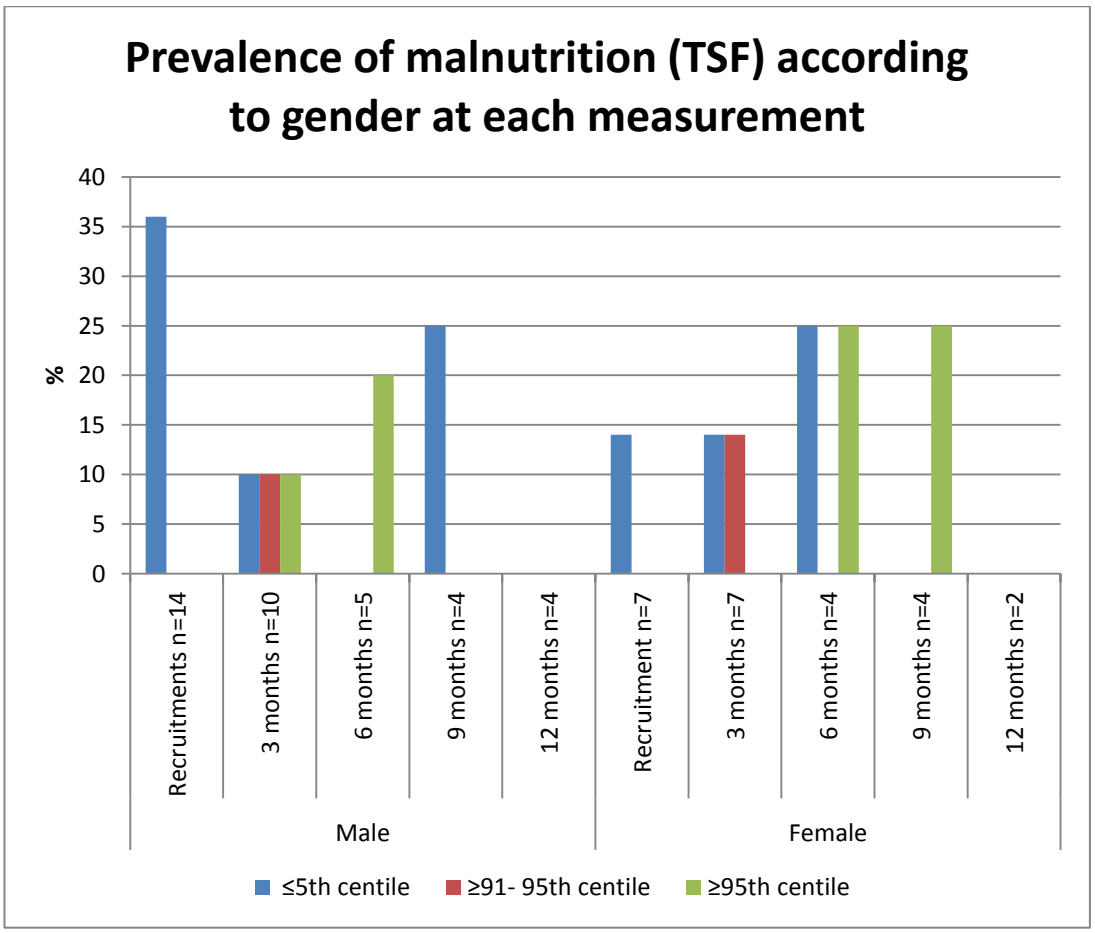


Figure 4.10 Prevalence of malnutrition according to gender at each measurement expressed as percentage (%). Undernutrition (TSF≤5th centile), overweight (TSF ≥ 91th/<95th centile), obesity (TSF≥ 95th centile).

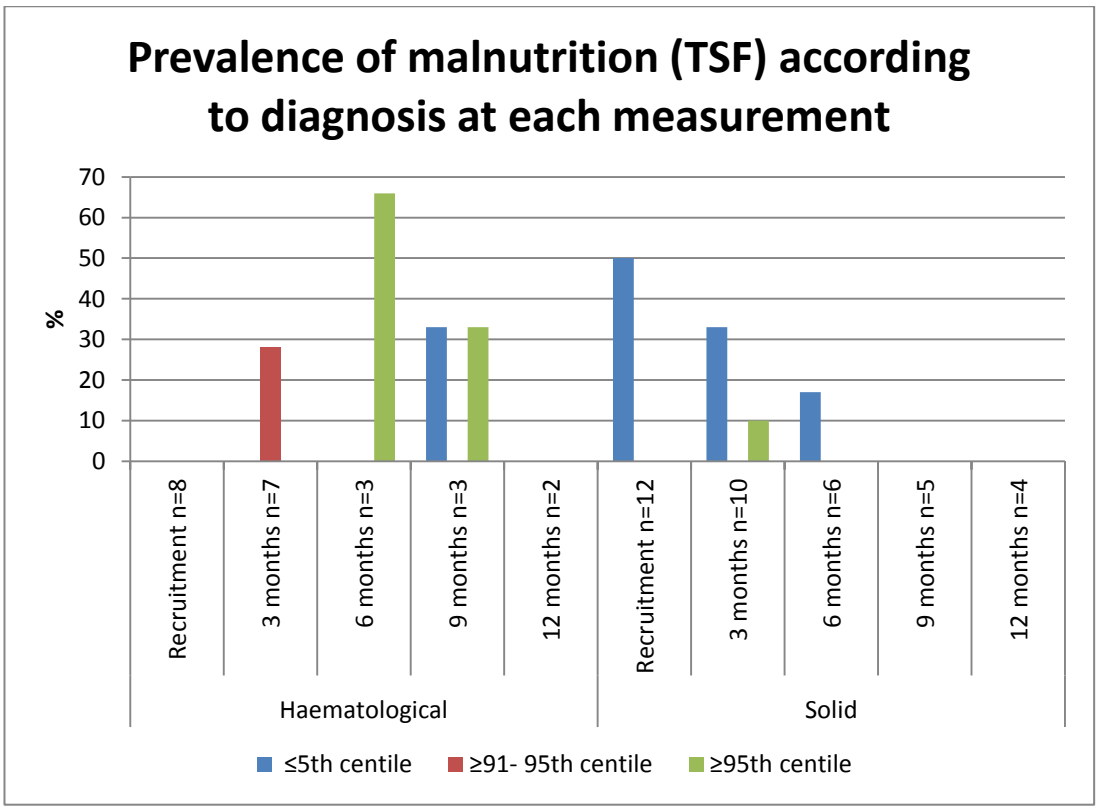


Figure 4.11 Prevalence of malnutrition according to diagnostic group at each measurement expressed as percentage (%). Undernutrition (TSF≤5th centile), overweight (TSF ≥ 91th <95th centile), obesity (TSF≥ 95th centile).

4.3.3 Bioelectrical impedance (BIA)

FM expressed as percentage of body weight was calculated from BIA measurements at each time point as explained previously (Section 4.2.7). FM% was significantly higher than reference standards (Fomon et al. 1982) for both genders ($p<0.05$) and diagnostic group ($p<0.05$) at every time point. The results showed a peak in FM% at six months in the haematological group (median 34.0%, IQR 28.9-38.9) and at nine months in the solid group (median 34.3 %, IQR 27.7-36.2). When stratified according to gender, FM% was highest in females at three months (median 37.2%, IQR 31.1-37.7) and at six months in boys (median, IQR 32.0 26.2-34.0; Table 4.5)

Table 4.5 Median (IQR) percentage of standard value (Fomon et al. 1982) at each time point for the entire according to gender and diagnosis. * p<0.05 measurement vs. standard

		Recruitment	3 months	6 months	9 months	12months
Male	FM%	28.9 * (20.1-34.3)	27.9 * (24.1-36.4)	32.0 * (26.2-34.0)	26.0 * (24.4-31.6)	25.7 * (23.4-28.7)
	Standard	17.5 (14.1-18.8)	17.5 (14.1-20.5)	17.5 (14.617.5)	16.7 (15.6017.6)	15.3 (14.3-15.9)
Female	FM%	31.5 * (30.4-32.2)	37.2 * (31.1-37.7)	37.1 * (29.3-44.0)	35.2* (32.7-36.7)	36.3* (34.7-37.9)
	Standard	23.7 (20.4-24.2)	24.0 (21.2-24.2)	21.9 (18.7-24.4)	21.6 (18.8-23.8)	21.1 (19.8-22.4)
Haematological	FM%	30.1 * (24.0-34.8)	28.0 * (25.4-35.1)	34.0 * (28.9-38.9)	25.1 * (23.8-35.2)	27.1 * (25.1-29.0)
	Standard	17.6 (14.6-19.3)	17.5 (14.6-20.9)	17.5 (16.1-17.6)	15.9 (15.3-16.8)	15.3 (14.9-15.6)
Solid	FM%	31.0 * (23.1-33.4)	33.0 * (25.3-38.7)	32.3 * (27.7-39.4)	34.3 * (27.7-36.2)	30.5 * (26.8-34.7)
	Standard	19.7 (14.3-23.8)	21.8 (18.0-24.1)	18.5 (16.7-23.0)	19.5 (17.5-23.7)	17.2 (15.3-19.8)

There was no significant association between FM% obtained from BIA and FM% (recruitment p>0.05, r= -0.61) or BMI centile (recruitment p>0.05).

There was no significant difference in FM% between genders or diagnostic group at any point in time. Because of the longitudinal design, the limited number of patients and the many drop offs, it was not possible to statistically analyse the changes FM%.

4.3.4 Comparison between incidence of undernutrition according to different assessment methods

Overall, the highest numbers of undernourished patients were reported by TSF (29%) and MUAC (24%). The Kappa limit of agreement test showed a poor agreement between BMI and both TSF (K 0.083 p<0.05), and MUAC (K 0.063, p<0.05) at recruitment, which suggests that MUAC and TSF identified more undernourished patients than BMI alone.

4.3.5 The use of nutrition support

Twenty one patients (81%) were referred to the oncology dietitian at some point during their cancer treatments. Of these cases, 15 (58%) were referred to the dietitian due to decreased oral intake or undernutrtion, and six (23%) for eating advice and/ or micronutrient supplementation.

15 patients (58%) were recorded as having a need for NS as defined by the use of OCS (n= 9, 35%) , ETF (n= 9, 35%) or PN (n= 1, 4%), or any combination of these. A PEG was inserted for three of these patients (12%). Two patients (8%) were treated in Dundee and their dietetic information was not available. Four (16%) of these patients received NS *via* more than one route through the course of their treatment. Ten patients (67%) receiving NS had solid tumours, representing 77% of all children diagnosed with solid tumours during the data collection period; five patients (33%) had haematological malignancies, representing 50% of those with this diagnosis in the cohort. Eight (53%) of all NS required advanced NS (ETF +/- PN).

Of those 15 patients requiring NS,Table 4.6 describes the use of NS according to the treatment modalities undergone.

Table 4.6 Distribution of the use of nutritional support according to treatment modalities

Treatment modality	Nutrition support Cases/total (%)	Frequency of route of NS			Advanced NS (% of total)
		OCS	ETF	PN	
Chemotherapy (13)	**9 (69)**	**7**	**4**	**0**	**4 (31)**
Chemotherapy and surgery (5)	**2 (40)**	**2**	**1**	**0**	**1 (20)**
Chemotherapy and radiotherapy (2)	**1 (50)**	**0**	**1**	**0**	**1 (50)**
Chemotherpy, radiotherapy and surgery (4)	**2 (50)**	**0**	**2**	**1**	**2 (50)**
Radiotherapy only (-)	**0 (-)**	**0**	**0**	**0**	**0 (-)**
Radiotherapy and surgery (-)	**0 (-)**	**0**	**0**	**0**	**0 (-)**
Surgery only (1)	**1/1 (100)**	**0**	**1**	**0**	**1 (100)**
No treatment(-)	**0 (-)**	**0**	**0**	**0**	**0 (-)**

For all treatment modalities the highest needs for NS were in the chemotherapy only group, chemotherapy and radiotherapy, and chemotherapy, radiotherapy and surgery, at 69 % and 50% respectively. Chemotherapy and radiotherapy, and chemotherpy, radiotherapy and surgery had the highest needs for advanced NS (ETF +/- PN) with 50% each.

4.3.6 Energy and macronutrient intake

4.3.6.1 Energy intake

Energy intake with NS and *ad libitum* intake was calculated to verify adequacy at the individual level. Energy intake both *ad libitum* and with NS was compared to the energy requirements for each subject using the Henry prediction equation (Henry 2005) adjusted for gender, age and physical activity. Table 4.7 shows the energy intake (kcal/d; median, IQR) *ad libitum* and with NS at each time point, according to diagnostic group and as percentage of energy individual requirements (Henry 2005). There were no significant differences between energy intake and energy

requirements according to gender or diagnosis (p>0.05). However, even though not significant, intake *ad libitum* expressed as percentage of EARs for the haematological group was higher (163%, IQR 131-196) than recommendations at recruitment (2076 kcal/d, IQR 1340-2525 vs. 1069 Kcal/d 1044 -1288, p>0.05) but lower (57%, IQR 46-62) at three months (928 kcal/d, IQR 906-1017 vs. 1532, IQR 1422-1896).

Similarly, intake with NS expressed as percentage of EARs for the haematological group was higher (163 %; IQR 141-196) than recommendations at recruitment (2076 kcal/d, IQR 1453-2525 vs. 1069 Kcal/d 1045 -1288 p>0.05) but lower (62%, IQR 46-72) at three months (1078 kcal/d, IQR 919-1206 vs. 1532, IQR 1423-1896). The daily energy intake expressed as a percentage of energy requirements was lower (p<0.05) in the haematological than solid group with both *ad libitum* food consumption and NS at three months.

Table 4.8 shows the energy (kcal/d) intake (median, IQR) *ad libitum* and with NS at each time point according to gender and as percentage of energy individual requirements (Henry 2005). However, even though not significant (p>0.05), energy intake *ad libitum* (930 kcal/d, IQR 888-1200) was much lower (63%) that requirements (1326 Kcal/d, IQR 1260-1513) in the male group at three months. This was not observed with NS (89%).There was no significant difference in daily energy intake expressed as percentage of energy requirements between the two genders.

Moreover, even though the energy intake *ad libitum* and with NS for the entire cohort and every subgroup were not significantly lower than energy requirements, few patients were identified as having their intake <80% of recommendation. The highest number of patients not meeting their requirements was observed at three months (n=8; 40%) followed by at six months (n=3; 27%).

Table 4.7 Energy (kcal/d) intake (median, IQR) *ad libitum* and with NS is shown at each time point according to diagnostic group. Energy intake *ad libitum* and with NS is also shown as a percentage of individual energy requirements. p<0.05 haematological group vs. solid group

	Time point	Energy requirement Kcal/d (Henry 2005)	Energy intake *ad libitum* Kcal/d	Energy intake *ad libitum* as % of EARs (Henry 2005)	Energy intake Kcal/d With NS	Energy intake with NS as % of EARs (Henry 2005))
Haematological	Recruitment n=10	1069 (1045-1288)	2076 (1340-2525)	163 (131-196)	2076 (1453-2525)	163 (141-196)
	3 months n=8	1532 (1423-1896)	928 (906-1017)	57 (46-62)*	1078 (919-1206)	62 (46-72)*
	6 months n=4	980 (925-1176)	1453 (1316-1577)	140 (125-148)	-	-
	9 months n=4	1448 (1375-1879)	2067 (1620-2641)	132 (81-193)	2100 (1762-2641)	146 (103-193)
	12 months n=3	1366 (1355-1414)	1231 (774-1573)	90 (57-111)	-	-
	15-18 months N=2	1388 (1377-1399)	1160 (939-1381)	83 (68-98)	-	-
Solid	Recruitment n=16	873 (463-951)	782 (321-1747)	136 (121-237)	1200 (866-1970)	194 (123-256)
	3 months n=12	1165 (620- 1340)	1214 (778-1316)	105 (91-178)*	1305 (901-1488)	115 (90-186)*
	6 months n=8	904 (827-1024)	1637 (1065-1835)	182 (101-209)	1677 (1359-1835)	182 (136-209)
	9 months n=6	1257 (1152-1374)	1125 (363-1308)	103 (26-128)	1173 (1013-1342)	107 (90-128)
	12 months n=4	1230 (1073-1375)	1254 (1130-1350)	111 (84-136)	-	-

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Table 4.8 Energy (kcal/d) intake (median, IQR) *ad libitum* and with NS is shown at each time point according to gender. Energy intake *ad libitum* and with NS is also shown as percentage of energy individual requirements.

	Time point	Energy requirement Kcal/d (Henry 2005)	Energy intake *libitum* Kcal/d	Energy intake at *libitum* as % of EARs (Henry 2005)	Energy intake Kcal/d With NS	Energy intake with NS as % of EARs (Henry 2005))
Male	Recruitment n=18	951 (877-1056)	1696 (1340-2525)	124 (72-150)	1453 (1069-2525)	171 (102-234)
	3 months n=13	1326 (1260-1513)	930 (888-1200)	63 (55-98)	1176 (930-1226)	89 (63-98)
	6 months n=7	980 (914-1083)	1595 (1400-1714)	152 (137-176)	-	-
	9 months n=5	1387 (1361-1509)	1807 (1714-2421)	133 (89-175)	1807 (1779-2421)	133 (118-175)
	12 months n=5	1366 (1343-1462)	1205 (906-1231)	84 (57-93)	-	-
	15-18 months N=2	1388 (1377-1399)	1160 (939-1381)	83 (68-98)	-	-
Female	Recruitment n=8	841 (656-1284)	782 (322-1331)	123 (122-144)	1129 (982-1569)	123 (79-127)
	3 months n=7	1080 (836-2305)	1213 (998-1255)	91 (67-164)	1446 (998-1680)	118 (56-187)
	6 months n=5	827 (812-947)	1065 (1049-1637)	168 (90-224)	1379 (1081-1677)	201 (95-224)
	9 months n=5	1153 (1152-1378)	1014 (146-1236)	90 (5-116)	1014 (1013-1333)	98 (88-116)
	12 months n=2	987 (9020-1073)	1396 (1350-1442)	144 (136-152)	-	-

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4.3.6.2 Protein, fat and carbohydrate intake.

Protein intake *ad libitum* and with NS was significantly higher than RNI at each measurement in each diagnostic group ($p<0.05$ for all; Table 4.9) and for both gender ($p<0.05$ for all; Table 4.10). CHO intake at each time point for the entire cohort and according to gender and diagnosis are shown in Figure 4.12. Fat as percentage of total energy intake/d according to gender and diagnosis is shown in Figure 4.13.

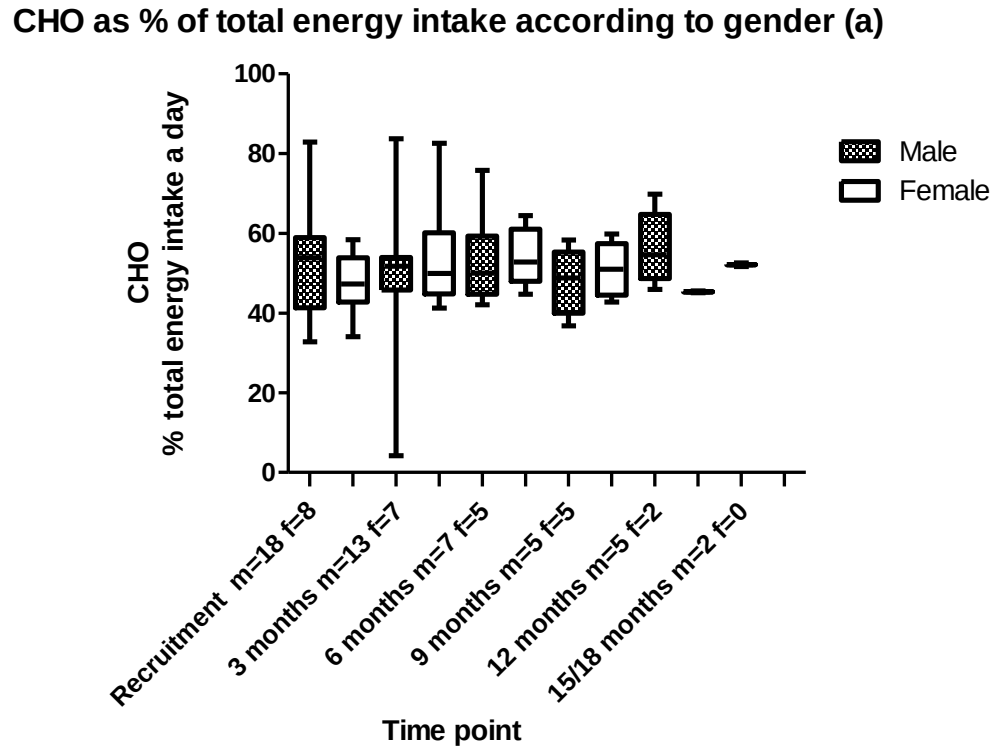
Althought fat intake as % of total energy intake for children over the age of five was higher than the reccomendations (35%) at three months (median 37.2, IQR 34.8-38.0), the difference was not statistically significant ($p>0.05$).There was no significant difference in fat or CHO intakes between the two diagnostic groups ($p<0.05$) or genders ($p<0.05$) at any time point.

Table 4.9 Median (IQR) protein intake g/d with NS and *ad libitum* according to gender

		Protein intake with NS g/d	**Protein intake *ad libitum* g/d**	**RNI (g/d)**
Male	Recruitment n=18	70.8 (45.8-95.6)	62.4 (29.1-95.6)	19.7 (14.5-28.3)
	3 months n=13	33.4 (17.0-46.5)	33.4 (14.0-44)	19.7 (14.5-28.3)
	6 months n=7	51.1 (41.2-52.0)	51.1 (41.2-52.0)	19.7 (15.8-26.1)
	9 months n=5	57.1 (56.7-85.9)	56.7 (56.4-85.9)	19.7 (14.5-19.7)
	12 months n=5	37.2 (35.5-49.1)	37.2 (35.5-49.1)	19.7 (19.7-19.7)
	15-18 months N=2	29.1 (28.3-29.8)	29.1 (28.3-29.8)	19.7 (19.7-19.7)
Female	Recruitment n=8	32.8 (25.8-54.0)	32.8 (25.8-54.0)	32.8 (25.8-54.0)
	3 months n=7	45.4 (31.4-58.0)	45.4 (31.4-58.0)	45.4 (31.4-58.0)
	6 months n=5	14.5 (14.5-36.7)	14.5 (14.5-36.7)	14.5 (14.5-36.7)
	9 months n=5	38.2 (30.0-41.5)	38.2 (30.0-41.5)	38.2 (30.0-41.5)
	12 months n=2	67.6 (59.9-75.2)	67.6 (59.9-75.2)	67.6 (59.9-75.2)
	Recruitment n=8	-	-	-

Table 4.10 Median (IQR) protein intake g/d with NS and *ad libitum* according to diagnostic group

		Protein intake with NS g/d	Protein intake *ad libitum* g/d	RNI (g/d)
Hematologic	Recruitment n=10	70.8 (63.8-101.3)	70.8 (60.0-101.3)	28.3 (19.7-42.1)
	3 months n=8	31.6 (25.9-47.6)	31.6 (25.9-35.6)	28.3 (19.7-42.1)
	6 months n=4	45.2 (35.5-53.3)	45.2 (35.5-53.3)	19.7 (18.4-25.3)
	9 months n=4	71.5 (56.9-90.7)	71.2 (55.8-90.7)	19.7 (19.7-25.3)
	12 months n=3	35.5 (25.9-45.9)	35.5 (25.9-45.9)	19.7 (19.7-19.7)
	15-18 months N=2	29.1 (28.3-29.8)	29.1 (28.3-29.8)	19.7 (19.7-19.7)
Solid	Recruitment n=16	45.8 (21.4-68.4)	31.7 (9.6-61.6)	19.7 (14.5-19.7)
	3 months n=12	44.7 (27.4-49.0)	40.7 (11.2-46.4)	14.5 (14.5-28.3)
	6 months n=8	50.7 (35.1-51.2)	38.5 (35.1-51.2)	14.9 (14.5-28.3)
	9 months n=6	39.9 (32.1-47.9)	41.5 (38.2-50.0)	14.5 (14.5-14.5)
	12 months n=4	50.7 (46.1-59.9)	17.1 (14.5-21.9)	17.1 (14.5-21.9)



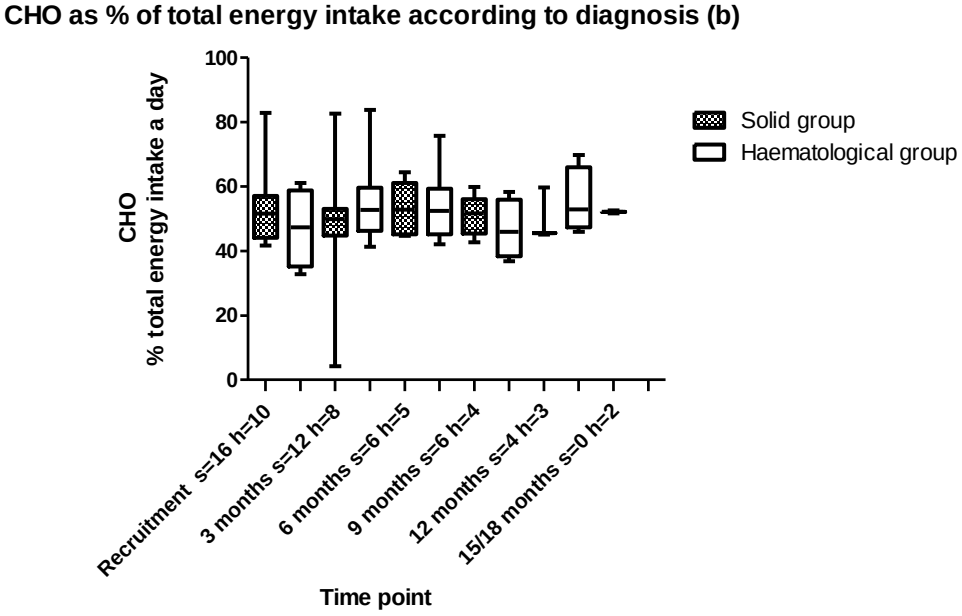


Figure 4.12 CHO intake with NS as percentage of total daily energy intake according to gender (a) and diagnosis (b).

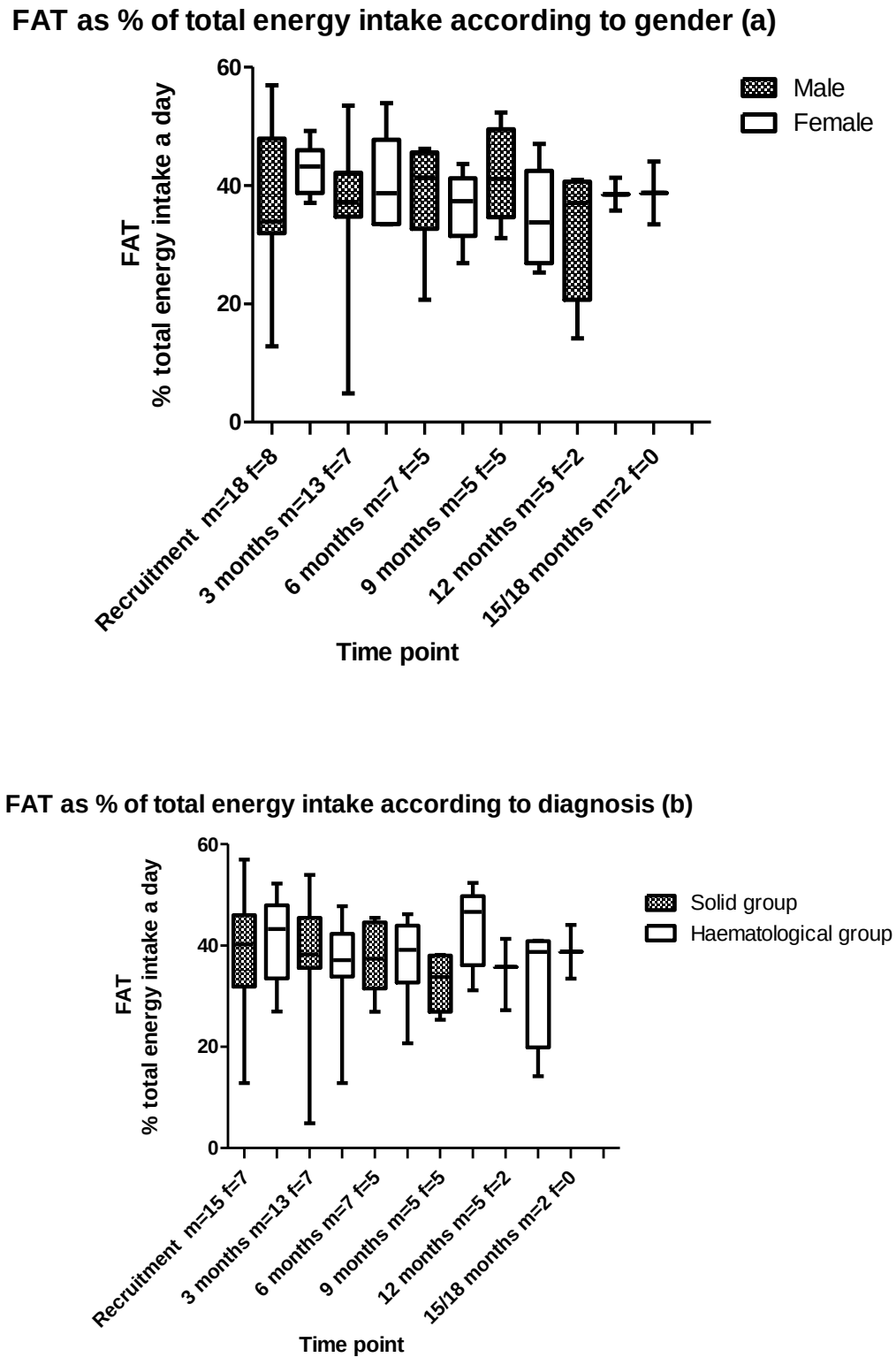


Figure 4.13 Fat intake with NS as percentage of total daily energy intake according to gender (a) and diagnosis (b).

4.3.7 Effectiveness of NS on counteracting undernutrition

The effectiveness of NS on counteracting undernutrition was tested by comparing mean BMI centiles before and after NS. On average, patients had an increased in BMI centile from initiation (median 17.0; IQR 3-48.5) to the end of NS (median 34.5; 10.2-59.5), but the changes were not statistically significant ($p>0.05$).

Median BMI centile was then compared according to the specific NS sub groups (OS and ENT). For the entire group of patients treated with NS the results showed a decrease in BMI centile from initiation (median 38.0, IQR 8.0 - 75.0) to the end of NS (median 32.0, IQR 10.0 - 91.0). However, this was not significant ($p>0.05$). On the other hand, for the entire group of patients treated with ENT the results showed a non-significant ($p>0.05$).increase in BMI centile from initiation (median 6.0, IQR 0.2 - 36.5) to the end of NS (median 37.0, IQR 37.0 - 53.5).

4.3.8 Physical activity

Of the 26 patients recruited five were ineligible for the physical activity monitor since they were too young to stand and walk by themselves. Of the 21 patients available only two patients decided to take part to this part of the study. Of these two, one patient did not wear the Actigraph and the device was lost. The other patients returned it but data was unreadable. The patient then became palliative and it was not possible to repeat the measurement. Therefore physical activity was not measured for any of the patients.

4.3.9 Biochemical profile

The results for the screening of blood parameters are reported in Table 4.11 (median; IQR). Interpretation of the data based on median values in this cohort is problematic because the reference ranges for many blood parameters varies depending on the age and gender of the patient. Therefore, Table 4.11 also shows the prevalence of patients with higher or lower values as percentages of total cohort, and numbers for each time point according diagnosis. The blood results were compared against the reference values in use at the RHSC Edinburgh.

4.3.9.1 Liver and renal function test

The overall liver function test (ALP, ALT, bilirubin and GGT) showed a damaging effect of treatments on liver function. In the solid group, alkaline phosphatase (ALP)

was below the normal ranges for age in 15% (n=2), 11% (n= 1), 30% (n=1) of patients at recruitment, three moths and nine months respectively. In addition, ALP was below the normal range in 30% (n=3) and 13% (n=1) of patients in the haematological group at recruitment and three months respectively.

Plasma alanine transaminase (ALT) was elevated in 15% (n=2), 11% (n=1) and 50% of patients in the solid group at recruitment, three months and six months respectively. In addition ALT was elevated in 60% (n=6), 38% (n=3), 25% (n=1) and 33% of patients in the haematological group at recruitment, three months, six months and 12 months respectively.

The bilirubin median was within normal ranges in both solid and haematological group at all measurements. Although bilirubin median was normal, 20% (n=2) and 25% (n=1) patients in the haematological group at recruitment and three months respectively had elevated plasma bilirubin.

G-glutamyl transferase (GGT) was elevated in 20% of patients in the solid group at recruitment and in 50% (n=1) and 25% (n=1) of patients at six months in the solid and haematological group respectively

Renal function assessment, showed that overall the patients in the study had electrolytes (potassium, sodium, magnesium) and plasma creatinine umol/l within the normal ranges for age for both solid and haematological groups at all measurements.

Plasma urea (mmol/l) was elevated in 50% (n=5) of the haematological patients at recruitment (mean 6.6, SD 2.4). Low plasma urea was found in 15% (n=2) and 33% (n=3) of patients with solid tumours at recruitment and three months respectively. In addition, low plasma urea was observed in 25% (n=1), 33% (n=1), 33% (n=1), and 50% (n=1) of patients with haematological cancers at six, nine, twelve and fifteen/eighteen months respectively.

4.3.9.2 Nutritional blood screening

All the subjects had adequate concentration of plasma vitamin E/cholesterol at all measurements. Plasma folate was within normal ranges for age for all patients in both groups at all measurements except for one haematological patient (25%), who was found to have plasma folate below the normal range at six months.

Plasma vitamin B_{12} was below normal range for 11% (n=1) and 33% (n=1) of solid tumour patients at three months and nine months respectively, and for 11% (n=1) and 33% (n=1) at recruitment and nine months respectively.

Plasma selenium was decreased in 16 % (n=2), 11 % (n=1) and 33% (n=1) of the solid tumour group at recruitment and three months, respectively. In addition one hematologic patient (13%) had elevated selenium at recruitment and 3 patients (43%) at three months.

Table 4.11 Blood screening presented as median (IQR) at each time point according to diagnostic group, with prevalence of patients with abnormal plasma levels: ↑ = higher that reference range, ↓ = lower than reference range, T = toxicity level, B = borderline low

			Solid			Haematological	
Test Normal range	**Measurement**	**n**	**Median (IQR)**	**Abnormal plasma level n (%)**	**n**	**Median (IQR)**	**Abnormal plasma level n (%)**
Albumin g/l							
birth-3months maturity dependent	Recruitment	12	37.0(34.0-38.0)	0(-)	7	5.9 (5.2-8.7)	0(-)
>3-12 months	3 month	9	39.5(34.0-40.25)	0(-)	7	6.7 (6.2-7.6)	0(-)
27.0-42.0	6 month	2	39.5 (37.2-41.75)	0(-)	4	5.4 (4.8-6.6)	↓1(25)
1-16 years	9 month	3	37.0 (34.5-38.0)	0(-)	3	4.9 (3.7-6.4)	0(-)
28.0-45.0	12 month	-	-	-	2	8.7 (7.2-10.1)	0(-)
*b borderline low is referred to those patients with albumin equal to the lowest normal value in the normal range	15/18 month	-	-	-	2	4.7 (4.1-5.2)	0(-)
Vitamin A µmol/l							
Birth – 12months	Recruitment	9	0.9 (0.7-1.3)	0(-)	9	304.0(255.0-465.0)	↓1(11)
0.5 – 1.5	3 month	8	1.2 (1.1-1.5)	↓1(11)	7	455.0 (310.0-636.0)	0(-)
1 – 7years	6 month	2	1.1 (1.0-1.2)	0(-)	4	364.0 (332.8-403.3)	0(-)
0.7 – 1.5	9month	2	1.3 (1.3-1.4)	↓1(33)	3	739.0 (371.6-762.0)	↓1(33)
7 – 13years	12 month	-	-	-	2	830.5 (616.3-1044.8)	0(-)
0.9 – 1.7	15/18 month	-	-	-	2	417.0 (416.5-417.5)	0(-)
13 – 19years 0.9 – 2.5 Toxic levels >3.3							
Vitamin D (25-Hydroxychole-calciferol) nmol/l	Recruitment	9	53.0 (21.0-73.0)	↓1(13)↑2(25)	8	3.2 (2.8-4.6)	↓1(13)
All ages	3 month	8	55.5 (45.8-82.0)	↓2(33)	3	2.4 (2.1-3.5)	0(-)
<25.0 deficient	6 month	2	30.0 (24.5-35.5)	0(-)	2	3.4 (2.7-4.2)	0(-)
25.0-49.0	9month	3	58.0 (42.5-81.5)	0(-)	3	1.4 (1.3-1.6)	↓2(67)
Borderline low. >50.0Adequate	12 month	-	-	-	2	2.7 (2.5-2.8)	0(-)
	15/18 month	-	-	-	2	4.5 (4.3-4.8)	0(-)

			Solid			Haematological	
Test Normal range	**Measurement**	**n**	**Median (IQR)**	**Abnormal plasma level n (%)**	**n**	**Median (IQR)**	**Abnormal plasma level n (%)**
Folate µg/l							
1 – 12months	Recruitment	5	16.5 (15.1-34.8)	0(-)	7	5.9 (5.2-8.7)	0(-)
>7	3 month	11	9.1 (8.0-12.1)	0(-)	7	6.7 (6.2-7.6)	0(-)
1-4years	6 month	2	15.1 (14.3-15.8)	0(-)	4	5.4 (4.8-6.6)	↓1(25)
4 – 30	9month	3	7.1 (5.5-11.2)	0(-)	3	4.9 (3.7-6.4)	0(-)
4-16years	12 month	-	-	-	2	8.7 (7.2-10.1)	0(-)
3 – 20	15/18 month	-	-	-	2	4.7 (4.1-5.2)	0(-)
Vitamin B12 ng/l							
0 – 5 years	Recruitment	8	565.5 (367.3-697.0)	0(-)	9	304.0(255.0-465.0)	↓1(11)
280 – 1400	3 month	9	521.0 (273.0-822.0)	↓1(11)	7	455.0 (310.0-636.0)	0(-)
5 – 16years	6 month	1	802.0 (-)	0(-)	4	364.0 (332.8-403.3)	0(-)
200 – 1100	9 month	3	728.0 (456.5-856.0)	↓1(33)	3	739.0 (371.6-762.0)	↓1(33)
	12 month	-	-	-	2	830.5 (616.3-1044.8)	0(-)
	15/18 month	-	-	-	2	417.0 (416.5-417.5)	0(-)
PTH pmol/l							
All ages 1.6 - 7.5	Recruitment	8	3.4 (2.9-14.0)	↓1(13)↑2(25)	8	3.2 (2.8-4.6)	↓1(13)
	3 month	6	2.3 (1.3-2.8)	↓2(33)	3	2.4 (2.1-3.5)	0(-)
	6 month	2	3.2 (2.9-3.4)	0(-)	2	3.4 (2.7-4.2)	0(-)
	9 month	3	3.5 (3.5-3.7)	0(-)	3	1.4 (1.3-1.6)	↓2(67)
	12 month	-	-	-	2	2.7 (2.5-2.8)	0(-)
	15/18 month	-	-	-	2	4.5 (4.3-4.8)	0(-)

↑= higher that reference range,↓ = lower than reference range, T = toxicity level, B = borderline low

			Solid			Haematological	
Test Normal range	**Measurement**	**n**	**Median (IQR)**	**Abnormal plasma level n (%)**	**n**	**Median (IQR)**	**Abnormal plasma level n (%)**
Calcium mmol/l							
Birth-7 days	Recruitment	13	2.3 (2.3-2.4)	↓1(8)	10	2.1 (2.1-2.2)	↓6(60)
1.6-2.7	3 month	9	2.4 (2.3-2.5)	↓2(22)	8	2.3 (2.2-2.4)	↓2(25)
7days-1 month	6 month	2	2.5 (2.4-2.5)	(0)	4	2.4 (2.4-2.4)	(0)
2.3-3.0	9 month	3	2.4 (2.4-2.4)	(0)	3	2.4 (2.4-2.5)	(0)
1-12 months	12month	-	-	-	3	2.4 (2.4-2.4)	(0)
2.3-2.8	15/18 month	-	-	-	2	2.3 (2.3-2.3)	(0)
1-16 years							
2.2-2.7							
Ferritin ug/l							
Birth-5 years	Recruitment	10	249.5 (135.5-886.5)	↑9(90)	9	449.0 (226.0-674.0)	↑9(100)
12.0-80.0	3 month	10	497.5 (41.0-952.0)	↑5(50)	8	1165.0 (665.8-2468.8)	↑8(100)
5-16 years	6 month	2	2434.5(1521.8-3347.3)	↑2(100)	4	1159.5 (724.8-2641.3)	↑4(100)
15.0-80.0	9 month	3	527.0 (296.0-996.5)	↑2(67)	3	1188.0 (906.5-1579.0)	↑3(100)
	12 month	-	-	-	2	609.5 (570.3-648.8)	↑2(100)
	15/18 month	-	-	-	2	426.0 (320.0-532.0)	↑2(100)
Selenium umol/l							
Birth - 2years	Recruitment	12	0.8 (0.7-0.9)	↓2(16)	8	1.4 (1.0-1.9)	↑1(13)
0.2 – 0.9	3 month	9	0.8 (0.7-1.0)	↓1(11)	7	0.7 (0.7-1.0)	↓3(43)
2 – 4years	6 month	2	0.8 (0.8-0.8)	0(-)	4	0.8 (0.8-0.9)	0(-)
0.5 – 1.3	9month	3	0.8 (0.7-0.9)	↓1(33)	3	0.9 (0.8-1.0)	0(-)
4 – 16years	12 month	-		-	2	1.0 (0.9-1.1)	0(-)
0.7 – 1.7	15/18 month	-		-	2	0.8 (0.8-0.8)	0(-)

↑= higher that reference range,↓ = lower than reference range, T = toxicity level, B = borderline low

			Solid			Haematological	
Test Normal range	**Measurement**	**n**	**Median (IQR)**	**Abnormal plasma level n (%)**	**n**	**Median (IQR)**	**Abnormal plasma level n (%)**
Cu µmol/l							
0-4 months	Recruitment	12	22.0 (18.8-27.9)	↑7(58)	8	10.8 (6.8-15.3)	0(-)
1.5-7.0	3 month	9	18.4 (17.3-23.0)	↑2(22)	7	17.6 (16.9-22.0)	↑2(29)
4-7 months	6 month	2	22.2 (22.1-22.2)	↑2(100)	4	18.2 (16.3-21.0)	0(-)
4.0-17.0	9month	3	21.1 (17.9-22.5)	0(-)	3	16.0 (13.5-19.0)	0(-)
8-12 months	12 month	-	-	-	2	14.9 (13.9-15.8)	0(-)
8.0-20.5	15/18 month	-	-	-	2	13.9 (12.4-15.5)	0(-)
1-6 years							
12.5-20.5							
6-10 years							
13.0-21.5							
10-14 years							
12.5-19.0							
>14 years							
Male 10.0-22.0							
Female 11.0-25.0							
Zn µmol/l							
All age	Recruitment	12	10.2 (9.8-10.9)	↓12(100)	8	9.3 (7.9-12.0)	↓6(75)
12.8-18.0	3 month	8	11.0 (10.2-11.1)	↓7(88)	7	10.1 (10.0-10.6)	↓7 (100)
	6 month	2	8.7 (8.4-9.1)	↓2(100)	4	12.0 (11.0-27.3)	↓2(50)
	9month	3	13.0 (11.0-13.2)	↓1(33)	3	11.0 (11.0-19.0)	↑1(33)
	12 month	-	-	-	2	12.0 (11.0-13.0)	(0)
	15/18 month	-	-	-	2	11.4 (11.3-11.6)	↓2(100)
HSCRP mg/l							
All ages <5	Recruitment	10	4.0 (2.0-13.3)	↑4(40)	9	2.0 (2.0-3.0)	↑2(22)
	3 month	9	2.0 (2.0-8.0)	↑3(33)	6	18.0 (2.0-37.0)	↑3(50)
	6 month	2	34.0 (20.5-47.5)	↑2(100)	3	2.0 (1.5-4.5)	↑1(33)
	9month	3	1.0 (1.0-2.5)	0(-)	3	1.0 (1.0-1.5)	0(-)
	12 month	-	-	-	1	2.1 (-)	0(-)
	15/18 month	-	-	-	2	1.0 (1.0-1.0)	0(-)

↑= higher that reference range,↓ = lower than reference range, T = toxicity level, B = borderline low

		Solid			Haematological		
Test Normal range	**Measurement**	**n**	**Median (IQR)**	**Abnormal plasma level n(%)**	**n**	**Median (IQR)**	**Abnormal plasma level n (%)**
Bilirubin umol/l							
All ages <20.0	Recruitment	12	4.5 (4.0-5.3)	0(-)	10	12.0 (9.5-16.3)	↑2(20)
	3 month	9	5.0 (3.0-9.0)	0(-)	8	7.0 (5.8-9.5)	0(-)
	6 month	2	9.5 (8.8-10.3)	0(-)	4	10.0 (8.3-16.8)	↑1(25)
	9 month	3	7.0 (4.5-8.5)	0(-)	3	6.0 (5.5-19.0)	0(-)
	12 month	-	-	-	3	7.0 (6.0-14.0)	0(-)
	15/18 month	-	-	-	2	5.5 (5.3-5.8)	0(-)
G-glutamyl transferase (GGT)units/l	Recruitment	13	18.0 (11.0-39.0)	↑3(20)	10	19.5 (14.0-30.5)	0(-)
Birth-2 months <200.0	3 month	9	24.0 (10.5-30.0)	0(-)	8	17.5 (17.0-21.3)	0(-)
1-16 years <40.0	6 month	2	107.0 (70.0-144.0)	↑1(50)	4	23.5 (14.3-35.5)	↑1(25)
	9 month	3	14.0 (12.5-17.0)	0(-)	3	12.0 (11.5-32.0)	0(-)
	12 month	-	-	-	3	13.0 (12.0-19.5)	0(-)
	15/18 month	-		-	2	9.5 (8.3-10.8)	
Alkaline phosphatase(ALP)							
birth – 1 month	Recruitment	13	133.0(118.0-180.0)	↓3(23)	10	115.5 (86.8-140.0)	↓3(30)
80 – 440	3 month	9	155.5 (122.3-194.8)	↓1(11)	8	129.0 (105.8-152.8)	↓1(13)
1 – 6 months	6 month	2	220.0 (215.5-224.5)	0(0)	4	161.0 (154.8-164.8)	0(0)
120 – 580	9 month	3	136.0 (112.5-142.5)	↓1(30)	3	159.0 (144.0-171.0)	0(0)
6 months – 1year	12 month	-	-	-	3	182.0 (163.5-187.0)	0(0)
110 – 430	15/18 month	-	-	-	2	170.5 (151.8-189.3)	0(0)
1 – 12years							
100 – 400							
12 – 16 years							
Males 100 – 400 Females 60 – 400							

↑= higher that reference range,↓ = lower than reference range, T = toxicity level, B = borderline low

			Solid			Haematological	
Test Normal range	**Measurement**	**n**	**Median (IQR)**	**Abnormal plasma level n(%)**	**n**	**Median (IQR)**	**Abnormal plasma level n (%)**
Alanine transaminase (ALT)							
unit/l	Recruitment	13	26.0 (22.0-36.0)	↑2(15)	10	62.0 (29.8-76.8)	↑6(60)
birth-12 months <65.0	3 month	9	28.0 (14.0-45.3)	↑1(11)	8	56.0 (32.5-103.0)	↑3(38)
1-16 years <50.0	6 month	2	77.5 (65.8-89.3)	↑1(50)	4	43.0 (28.5-77.5)	↑1(25)
	9 month	3	15.0 (12.5-22.5)	0(0)	3	28.0 (21.0-31.5)	0(0)
	12 month	-	-	-	3	19.0 (17.5-46.0)	↑1(33)
	15/18 month	-	-	-	2	19.0 (16.5-21.5)	0(0)
Urea mmol/L							
2 weeks-1month	Recruitment	13	3.5 (2.6-4.4)	↓2(15)	10	7.8 (4.7-8.8)	↑5(50)
0.08-0.39	3 month	9	3.1 (2.0-4.3)	↓3(33)	8	3.9 (3.2-4.2)	0(-)
1 months-12months	6 month	2	4.2 (3.3-5.0)	0(-)	4	3.5 (3.1-3.8)	↓1(25)
1.2-5.0	9 month	3	2.8 (2.8-3.0)	0(-)	3	4.0 (3.1-5.0)	↓1(33)
1-16 years	12 month	-	-	-	3	3.7 (2.9-4.7)	↓1(33)
2.4-6.5	15/18 month	-	-	-	2	3.1 (2.2-3.9)	↓1(50)
Phosphate mmol/l							
1-12 months	Recruitment	13	1.4 (1.1-1.6)	↓2(15)	10	1.1 (1.0-1.3)	↓1(10)
0.8-2.6	3 month	9	1.4 (1.3-1.5)	0(0)	8	1.5 (1.4-1.6)	0(0)
1-16 years	6 month	2	1.5 (1.3-1.6)	0(0)	4	1.6 (1.5-1.7)	0(0)
1.0-2.1	9 month	3	1.6 (1.3-1.6)	0(0)	3	1.5 (1.3-1.6)	0(0)
	12 month	-	-	-	3	1.6 (1.5-1.6)	0(0)
	15/18 month	-	-	-	2	1.6 (1.5-1.6)	0(0)

↑= higher that reference range,↓ = lower than reference range, T = toxicity level, B = borderline low

4.3.9.3 Vitamin D, PTH and calcium axis

Median levels of plasma 25(OH) D, the prevalence of vitamin D deficiency and borderline low according to plasma 25(OH) D concentrations are shown in Table 4.12.

Table 4.12 25 (OH) D nmol/l plasma concentration (median IQR) and prevalence of vitamin D deficiency (plasma 25(OH) D < 25 nmol/l) and borderline low (plasma 25(OH) D >25 <50 nmol/l) at each measurements.

Measurement	Deficiency (plasma 25(OH) D < 25 nmol/l)	Borderline low (plasma 25(OH) D >25 <50 nmol/l)	Median (IQR)
Diagnosis (n=16)	31% (n=5)	44% (n=7)	40.0 (23.0-71.0)
3 month (n=14)	14% (n=2)	43% (n=6)	49.0 (44.5-66.0)
6 month (n=3)	33% (n=1)	67% (n=2)	40 (34-46.25)
9 month (n=6)	-	16.7 % (n=1)	56.5 (45.0-69.5)
12 month (n=2)	-	-	69.0 (63.0-75.0)
15/18 month (n=1)	-	100 (n=1)	23.0 (19.0-28.5)

The difference between plasma 25(OH) D in the two diagnostic groups was not significant at any measurement ($p > 0.05$). However, the prevalence of vitamin D deficiency at diagnosis was higher in the solid tumour group (44%) compared to the haematological group (29%). At three months 33% of haematological group were vitamin D deficient compared to 0% for the solid tumour group. There was no statistical difference ($p>0.05$) between the plasma 25(OH) D (nmol/l) during summer months (beginning of May to the end of September: recruitment median 44.0, IQR 25.8-75.7, three month median 39.0, IQR 18.8-101.2) and winter months (recruitment median 38.5, IQR 16.0-53.5; three month median 51.0, IQR 47.5-51.0).

Vitamin D status has been reported to negatively correlate with BMI (Baradaran et al. 2012; Goshayeshi et al. 2012; Zwart et al. 2011). However, the non significant association between BMI and centile at baseline and vitamin D status was observed in the current population. However, from the graphical representation (Figure 4.14),

it is apparent that low plasma 25(OH) D was associated with both very low and very high BMI centiles.

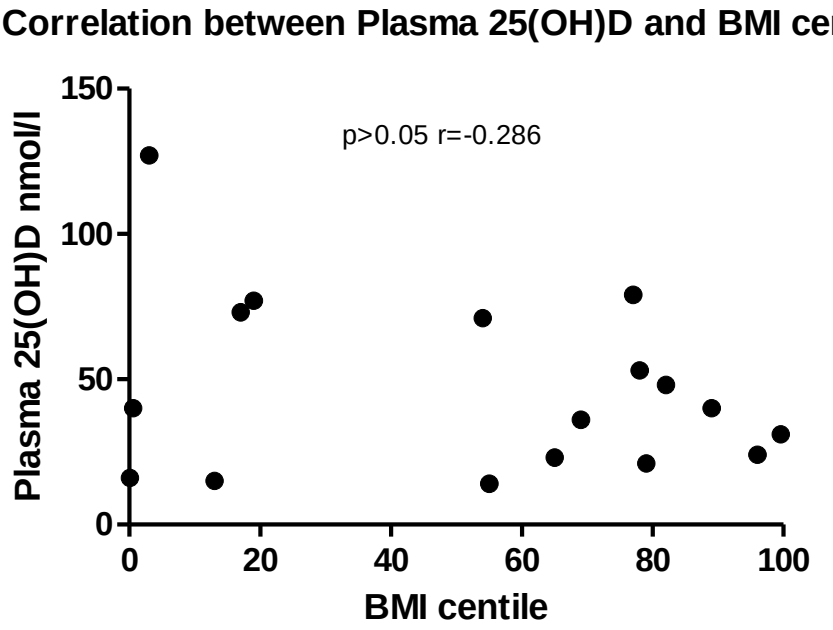


Figure 4.15 Correlation between BMI centile and plasma 25(OH) D at baseline

Reporting of the results for vitamin D took between two to three months from the time of the blood tests. Therefore vitamin D supplementation was initiated based on these results, but took several months to begin. During data collection vitamin D supplements (10 µg /d ergocalciferol) were prescribed to seven patients after being found to have hypovitaminosis D. Only two patients supplemented with vitamin D in this period, had plasma 25(OH) D available before and after intervention. For both patients, plasma 25(OH) D increased up to the normal range.

Because of the effect of low plasma 25 (OH) D on PTH secretion and bone turnover, plasma PTH was also measured. Of the patients with vitamin D deficiency at diagnosis, 50% had secondary hyperparathyroidism. Hyperparathyroidism was not present thereafter. Hypoparathyroidism presented in 13 % of both solid and haematological cases with normal concentrations of plasma 25(OH) D. There was no statistical difference in plasma PTH at any of the time point ($p>0.05$). Neither was

there any significant correlation between PTH and 25(OH) D variables (p>0.05) at any point in time (Figure 4.16).

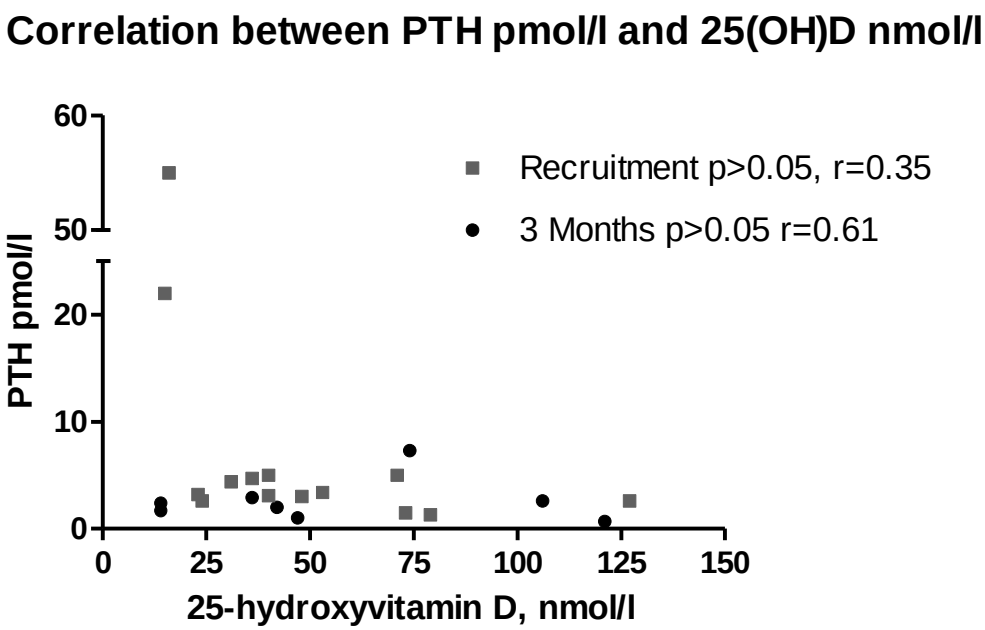


Figure 4.16 Relationship between 25- hydroxyl vitamin D and PTH.

Because of the role of vitamin D in calcium absorption and metabolism, calcium was also measured. Plasma calcium according to diagnostic group is shown in Table 4.11. Of the patients with solid and haematological cancers, 8% and 60% respectively had low plasma calcium upon recruitment. Moreover, 22% and 25% of patients with solid and haematological cancers respectively had low plasma calcium at three months. Plasma calcium was within the normal ranges after this point (Table 4.11). Comparison between the solid and haematological group was not possible because of the difference age ranges and the small sample size.

Figure 4.17 shows the relationship between plasma calcium and 25(HO) D at recruitment and three months. There was no significant correlation between the two variables (p>0.05). However, many patients with low plasma 25(OH) D, had plasma calcium below the normal ranges.

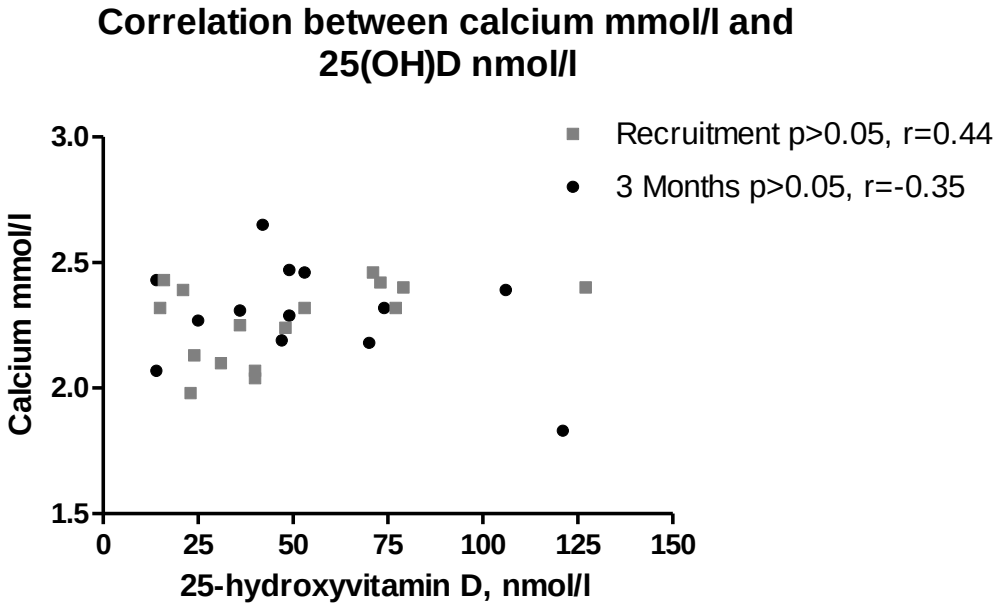


Figure 4.17 Relationship between plasma calcium and 25-(OH) D. The patients with plasma calcium between 2.2 and 2.3 and 25-(OH) D below 50 mmol/l were older than one year therefore within the normal values.

Low plasma phosphate can be caused by vitamin D deficiency. At recruitment phosphate (mmol/l) was below normal ranges for age, for 15% (n=2) patients in the solid group and 10% (n=1) patients in the haematological group. There was no significant correlation between the two variables (p>0.05) at any point in time. However, the patients with low plasma 25(OH) D had also plasma phosphate below normal.

4.3.9.4 Serum vitamin A supplementation and toxicity.

Plasma vitamin A was elevated but below toxicity levels in 11% (n=1) of patients in the solid group at recruitment and 26% (n=2), and 25% (n=2) of patients in the solid and haematological group respectively, at three months. The patients with elevated vitamin A were not supplemented with vitamins at the time of measurement and plasma vitamin A returned within normal ranges thereafter. However, plasma vitamin A was below normal ranges in 25% (n=2) in the haematological group at three months. During data collection four patients were supplemented with a multivitamin solution for children (ABDEC, Parke-Davis/Pfizer) containing retinol

as vitamin A palmitate, at 733 mg/ day for children and 362.5 mg/d for babies. One of the supplemented patients had elevated vitamin A before starting supplementation. Of the four supplemented patients, plasma vitamin A was only available for two patients, because one started supplementation after the last blood test recorded and one did not have further blood test carried out after supplementation was started.

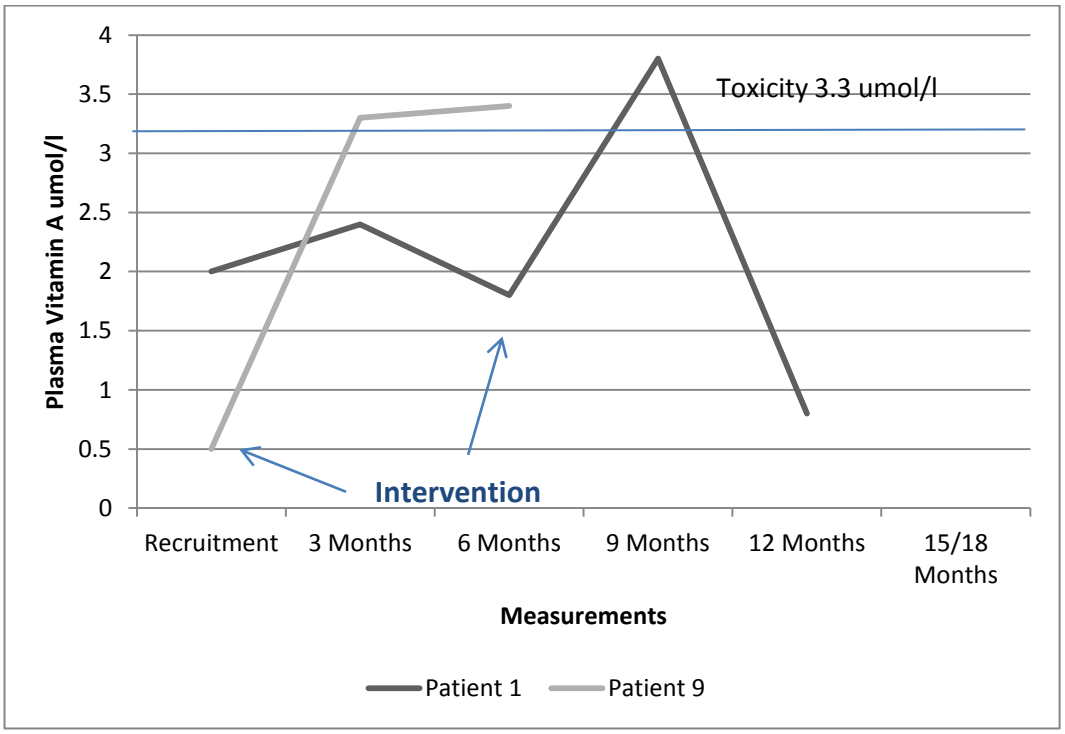


Figure 4.18 Vitamin A plasma levels in the two supplemented patients.

Figure 4.18 shows vitamin A plasma levels in the two supplemented patients. Supplementation started after the third month for patient 9 and after the ninth month for patient 1. Remarkably plasma vitamin A reached toxicity level after three months supplementation, upon which point supplementation was stopped. Plasma vitamin A returned to normal in patient 1 after supplementation was stopped. It was not possible to assess plasma vitamin A after the supplementation was stopped for patient 9 because the blood was not collected thereafter.

4.3.9.5 C reactive proteins, albumin copper, zinc, selenium and ferritin

Median hsCRP mg/l (Table 4.11) was above the normal range in the solid group at six months (median 34, IQR 20.5-47.5) and in the haematological group at three months (median 18, IQR 2.0-37.0). In the solid cancer group, 40% (n=4), 33% (n=3) and 100% (n=2) of patients had elevated plasma hsCRP at recruitment, three months and six months respectively. Similarly, in the haematological malignancies group, 22% (n=2), 50% (n=3) and 33% (n=1) of patients had elevated plasma hsCRP at these time points.

At recruitment, albumin was borderline low in 15% (n=2) patients in the solid group and in 33% (n=3) patients in the haematological group. Serum albumin returned to normal at three months.

Zinc was decreased in both groups at each measurement apart in the haematological group at 12 months when plasma zinc was within normal range, and with one haematological patient observed to have high levels at nine months. Ferritin was elevated in 100% of haematological patients at each measurement and in 90% (n=9), 50% (n=5) 100% (n=2), 67% (n=2) of the solid group at recruitment, three months, six months and nine months respectively.

In order to assess whether low serum levels of albumin, Se and zinc and elevated serum copper and ferritin were caused by inflammation they were then analysed in relation to increased plasma hsCRP. Table 4.13 shows the numbers and percentage of patients with levels of albumin, Se, copper, zinc and ferritin seen in acute phase response in relation to hsCRP.

Table 4.13 Number and % of patients with abnormal plasma value which also had hsCRP above normal range

	Recruitment n (%) with hsCRP >5 mg/L	3 Months n (%) with hsCRP >5 mg/L	6 Months n (%) with hsCRP >5 mg/L	9 Months n (%) with hsCRP >5 mg/L	12 Months n (%) with hsCRP >5 mg/L	15/18 Months n (%) with hsCRP >5 mg/L
↑Albumin	2 (40) 2 CRP not available	-	-	-	-	-
↓Selenium	1 (50)	2(50) 2 CRP not available	-	0(-)	-	-
↓Zinc	3 (25) 3 hsCRP not available	6 (43) 2 hsCRP not available	3(75) 1 hsCRP not available	-	-	-
↑Copper	4(36) 1 hsCRP not available	4(100)	4(100)	-	-	-
↑Ferritin	5(28)	6(46) 2 hsCRP not available	3(50) 1 hsCRP not available	0(-)	0(-) 1 hsCRP not available	0(-)

Many hsCRP values were missing. However, this comparison shows that between 25% and 100% of the abnormal levels of those acute phase reactants occurred at elevated plasma hsCRP concentration.

4.4 Discussion

The current study has prospectively examined the changes in nutritional status with simultaneous anthropometry, BIA, and dietary intake in children with several types of cancer, from diagnosis. This study followed the patients for an extended period of time, from diagnosis through the progression of disease. Therefore, it allowed analysis of changes in nutritional status in response to treatment, and nutritional intervention.

In the current investigation, the risks for both undernutrition and obesity were explored. Despite the strong evidence of an increased risk of undernutrition during cancer therapy, the evidence base on nutritional care in children and young people with cancer is scarce and fragmented. Moreover, despite strong evidence to show an

increased risk of late onset of obesity in this cohort, little attention has been paid to the clinical management of obesity during childhood cancer therapy. The causes of obesity in this cohort remain unclear. Therefore understanding the factors that contribute to the development of malnutrition, both undernutrition and obesity will prove central in the better nutritional management during childhood cancer therapy.

A novel aspect of this study is that it longitudinally investigated the micronutrient status during childhood cancer therapy. This study showed that micronutrient status can be negatively affected during treatment for childhood cancers. The evidence generated in this study suggests that micronutrient status should also be a focus of nutritional care in this patient group.

4.4.1 Study population

An average of 55-60 patients is referred to the oncology/haematology team at the RHSC in Edinburgh every year. During the 18 month data collection period of the current study, only 64 patients were referred to the oncology/haematology service, which is a third smaller than average recorded by the service. Of those patients, 13 were not diagnosed with cancer and hence discharged from the service. Only 51 were diagnosed with childhood / teenager cancer, or with benign brain tumours, of which a third did not meet the inclusion criteria for different reasons. Many patients with benign brain tumours were diagnosed after they were discharged and did not go back to the service for many months. Hence, they were considered ineligible as they did not have any on-going care. A few patients were palliative or died soon after they were diagnosed, and could not be included in the study. Other patients were unsuitable because of social circumstances, as one of the parents was in palliative care. Finally a patient was considered unsuitable due to clinical reasons as advised by the consultants.

Of those eligible, a quarter did not take part to the study because they felt it was to stressful at the time. Because of the study design and its prospective nature, the patients and their families were approached soon after diagnosis, when advised appropriate by the oncology/haematology team. However, this period is extremely traumatic for the family and they are overwhelmed with information regarding the

diagnosis and the treatments to follow. Furthermore, there are other priorities such as deciding whether to participate to a clinical trial. Clinical trials are standard care in the treatment of childhood cancer, and the decision to join a clinical trial must be made very rapidly after diagnosis. There are both benefits and risks of taking part in a clinical trial; hence making the decision can be quite stressful for the families.

Because of the above reasons, this study had been sometimes perceived as additional stress for something which would not have benefit for the patient. Even thought the importance of research and the role of nutrition in cancer care were comprehensively explained at recruitment, the recruitment rate is reflective of the nature of the disorder. The recruitment ratio was comparable to recruitment of a previous study carried out in the same cohort (Reilly et al. 2001).

The most common diagnosis in this prospective cohort was leukemia followed by the soft tissue sarcoma and neuroblastoma. The incidence of each type of childhood cancer does not appear to reflect the incidence in the UK population (Cancer Research UK 2012) or Scottish population (Information Service Division Scotland 2012). Because of the small sample size and low recruitment rate, some diagnosis were missing from this cohort such as bone, epithelial and haepatic cancers.

The results of the prospective study showed unequal distribution of childhood and teenage cancers between the genders, which does not reflect the national data (Cancer Research UK 2012; Information Service Division Scotland 2012). This discrepancy is likely to be caused by the small sample size and by the high percentage of patients with ALL, as this particular diagnosis is more common in boys than girls. The age distribution was comparable to the data collated by Cancer Research (Cancer Research UK 2012) with some cancers such as leukaemia and soft tissue sarcoma having the highest incidence rate in the first few years of life, and lymphomas having the peak in adolescence (Information Service Division Scotland 2012). However, when analysed according to the more general definition of haematological and solid tumours, the data reflected the national population (Cancer Research UK 2012; Information Service Division Scotland 2012). Furthermore, this

study covered similar age groups to the published literature that included all the childhood cancer diagnosis (Pietsch and Ford 2000; Smith et al. 1991).

The survival rate was analysed at the last collection point. However, in comparison to the national data was not possible because the data on survival are generally based on five year survival (Cancer Research UK 2012; Information Service Division Scotland 2012), whereas the survival rate in this study was recorded between a minimum of two months from diagnosis to maximum 18 months. Due to the limited numbers available and the extent of protocols and regimens used to treat childhood cancer, it was not possible in this study to analyse the data according to treatment protocol. The treatments were therefore categorised according to more general definitions.

The diagnostic information on the patients who refused to participate could not be recorded for ethical reasons. Therefore, it was not possible to assess whether their demographic and diagnosis reflected those of the participants, and it was not possible to statistically establish if a selection bias was present.

In this current study, patients with a diagnosis associated with high nutritional risk (Betcher and Ablin 1993; Han-Markey 2000; Rickard et al. 1986), were either diagnosed in the final months of the study, or became palliative very quickly; therefore, they could not be monitored for an extended period. Consequently, some extent of bias may have been introduced, and it could be possible that the observation in this study may be responsible for underestimating the risk of undernutrition.

4.4.2 Nutritional status

The assessment of nutritional status is essential in the nutritional management of children treated for cancer. However, it has been proven difficult because of the limitation of the assessment methods in this particularly cohort. Studies of nutritional status of children have been based on a variety of anthropometric measurements such as arm anthropometry, BMI centile and BIA. The aim of this current study was to prospectively assess nutritional status changes and the prevalence of malnutrition

(both undernutrition and overnutrition) using BMI centiles, MUAC, TSF and BIA techniques. This has allowed a more comprehensive assessment of nutritional status and the evaluation of the differences in measurements in this specific cohort.

This current study showed that the highest prevalence of nutritional deprivation was among the solid group with BMI centile median below the 50th centile for the first nine months of treatments. The low BMI centiles were associated with an increased prevalence of undernourished children compared to the expected prevalence of undernutrition for the UK population (Department of Health 2012). In contrast, the haematological group had a BMI centile median above the 50th centile for the first nine months of treatment, and none of the patients were classified as undernourished. Although, the prevalence of obesity and overweight observed in the current study among the haematological group was higher that the expected prevalence for the UK population, the difference was significant only at six months. The lack of significance is likely to be caused by the small sample size.

When the cohort was stratified according to gender it become apparent that both boys and girls had a higher prevalence of undernutrition at diagnosis compared to the expected prevalence for the UK population. In contrast, the prevalence of obesity and overweight was comparable to the expected prevalence for the UK population.

Due to the limited numbers and the many drop outs it was not possible to statistically analyse the changes over time by ANOVA. Although the median and the percentages provide important information in respect to a specific time point, it is not possible to draw any conclusions regarding changes over time. Thus, the data from this study can only be interpreted in relation to each individual time point.

The variance observed in BMI centiles in this study could put doubt on the interpretation of the results. However, because the cohort were children treated for cancer, the degree of variation observed is likely to be a reflection not only on the cancer and its treatments on nutritional status, but also the small sample size. BMI centiles are based on reference data and interpretation of the data requires a degree of confidence on the adequacy of the standard used. In this study the revised version of

the 1990 UK reference value (Cole et al. 1995) was used which have been reported to be adequate to assess growth in children (Savage et al. 1999). Therefore, the use of this reference was believed not to be a concern when the study was designed. However, in 2011 new standards for children 0-4 years were adopted (RCPCH 2011) which closely reflects the current UK recommendations for infant feeding. They are believed to be more appropriate for growth monitoring (SACN/RCPCH 2007).

It has been reported that the new reference data identifies fewer children as underweight, but it is likely to identify more obese children (SACN/RCPCH 2007). Therefore, it could be argued that the prevalence of malnutrition observed in this study may not represent the cohort accurately and that this current study may have overestimated undernutrition and underestimated obesity. However, when the prevalence of malnutrition is considered in conjunction with arm anthropometry it appears that BMI centiles alone tend to underestimate the prevalence of undernutrition.

Additionally, malnutrition was assessed using BMI centile cut off points. There are a number of thresholds to which BMI can be compared to and it is unknown which one is the most suitable for children with cancer. Recently the SACN/RCPCH (2011) recommended < 2.3nd centile as cut off point for undernutrition for children 2-18 years. This value corresponds to -2SDS and it has been widely used in the literature to assess undernutrition in children with cancer (Pietsch and Ford 2000; Reilly et al. 1999). However, WHO recommend a more rigorous definition of undernutrition in adolescents as BMI below the 5thcentile (World Health Organisation 1995). Moreover some authors have employed an even more severe definition of undernutrition (<15th centile= moderate undernutrition; <5th severe undernutrition) (Sala et al. 2012). This inconsistency in the threshold used to assess undernutrition for the general population casts into doubt the adequacy of these cut off points to assess undernutrition in children during cancer therapy. It has been shown that most undernutrition related mortality occurs with both mild and moderate undernutrition (Pelletier and Frongillo 2003). Therefore, if the likelihood of a rapid nutritional deterioration during cancer therapy is also considered, it may be important to

distinguish between grades of undernutrition during childhood cancer treatments and to use more rigorous definition of undernutrition.

Another limitation of the use of BMI centiles to assess nutritional status during cancer treatments is the accuracy of the height and weight measurements. However, in this study the observers' TEM was shown to be low. Therefore, it is unlikely to have influenced the results and conclusions drawn in this study. However, if the TEM influenced the results, it would have increased the variance but would have not biased the results.

The findings in this study support the observation that nutritional depletion is common during treatment for solid cancer especially at diagnosis (Garofolo et al. 2005; Smith et al. 1991). On the other hand, nutritional depletion appeared to be uncommon in children in the haematological group in this study. Although undernutrition is a well known problem at diagnosis in solid cancer patients, the evidence for undernutrition in haematological patients remains controversial.

Comparison of the findings of this study and the prevalence of undernutrition reported in other studies is difficult due to the variation in the diagnosis studied, the anthropometrical parameters used and the cut off points used to define undernutrition. Several authors have reported no indication of nutritional deprivation in children treated for ALL at diagnosis (Uderzo et al. 1996) or during treatment (Delbecque-Boussard et al. 1997) when compared against healthy subjects. However, others (Reilly et al. 1999; Yu et al. 1994; Yu et al. 1994) have identified poor nutritional status at diagnosis.

Reilly et al. (1999) showed a significant increase in the prevalence of undernutrition assessed by BMI SDS compared to the expected frequencies for the UK population in a cohort of 1019 patients. Although the study (Reilly et al. 1999) used comparable methodology to this current study, the results are in contrast. This is probably due to the small sample size in this current study. Moreover, Reilly et al. (1999) were likely to have included a broader variety of ALL risk groups, and hence to have included patients with high risk ALL which are at higher risk of nutritional deprivation

(Betcher and Ablin 1993; Han-Markey 2000; Rickard et al. 1986). This group were not present in the current study. Another important aspect that may have affected the results in the current study is the masking effect of obesity on undernutrition. BMI centiles should be interpreted in relation to pre-illness weight and weight loss. However, in the current study, this information was not recorded, mainly because most of the parents were unable to recall the information. Therefore, although 25% of the haematological patients were classified as obese by BMI centiles at diagnosis, they might have been undernourished if assessed using a weight loss parameter.

A unique aspect of the current study is the assessment of the prevalence of overweight and obesity during childhood cancer treatments. Previous studies have documented the increased risk of obesity during both treatment (Odame et al. 1994; Reilly et al. 2000; Reilly et al. 1996; Van Dongen-Melman et al. 1995) and in later life (Dalton et al. 2003; Meacham et al. 2005; Oeffinger et al. 2003; Warner et al. 1995). Although, the observed increase in the prevalence of obesity in this study is in line with the literature, quantitative comparison is very difficult. For example, Reilly et al. (2000) reported an increased prevalence of obesity measured as BMI SDS > 2, from 5% at diagnosis, to 4% at one year and 9% at three years, in 98 newly diagnosed ALL patients. However, these figures are much lower that those observed in the current study. This inconsistency is likely to be caused by the small sample size in this cohort. The small sample size is also likely to have caused the lack of significance observed when the cohort was compared to the UK prevalence of obesity. However, although not significant, this finding highlights the issue of excess body weight during treatment for ALL and should not be underestimated.

It has been previously suggested that cranial radiotherapy, may cause increased energy intake or/and reduced REE (Groot-Loonen et al. 1996; Odame et al. 1994; Oeffinger et al. 2003). However, in the past 20 years CRT is not given routinely, and no patients in this current study were treated with CRT. Therefore, CRT can not be an underlying cause of the excess fat gain observed in this study. A study in ALL patients experiencing excess weight gain showed that the positive energy balance was not caused by decreased REE (Reilly et al. 1996), and recently, reduced physical

activity has been recognised as the main cause of reduced energy expenditure (Reilly et al. 1998). Moreover, steroid therapy leads to an increase in energy intake during ALL treatments, contributing further to the positive energy balance (Reilly et al. 2001). Therefore, the excess body weight and fat deposition observed in this study is likely to be a consequence of steroid treatment and reduced physical activity. However, in this study physical activity was not measured due to the lack of patient compliance. Consequently, the contribution of reduced physical activity on excess weight gain is unknown.

Reilly et al. (2000) identified low BMI SDS at diagnosis, and young age as risk factors for excess weight gain during ALL treatments. These patient characteristics at diagnosis are routinely measured and recorded during the clinical management of ALL. Therefore, they could form the basis for targeting a prevention programme. However, in the current study, due to the limited sample size, it was not possible to test the influence of those factors on excess weight gain. Moreover, none of the patients in this current study had particularly low BMI at diagnosis.

In the current study, TSF and MUAC measurements were used to estimate energy stores of subcutaneous fat, and protein reserves stored as lean body mass during treatments. This research showed that BMI changes overtime were associated with anthropometrical changes that were outwith the technical error of measurement of the researcher. Arm fat mass centile correlated with BMI centiles.

Although not statistically significant, this study showed that the solid tumour group had depleted fat stores during the first three months of treatments, with upper arm fat area values decreasing from 78% at diagnosis to around 70% of standard at three months. Fat stores returned to normal levels by six months. On the other hand, haematological patients had excess fat reserves during treatments. Upper arm fat area, expressed as percentage of standard value, reached a peak at three months after diagnosis, with a value of 130% of standard. Similarly, the muscle reserves were at their peak at three months (134% of standards). Interestingly, arm muscle mass decreased by up to 88% of standards after nine months of treatment. The prevalence of obesity peaked at three months with more than 60% of the haematological patients

having their TSF and MUAC over the 90th centiles. A very interesting finding of this study is that none of the haematological patients was classified as undernourished by arm anthropometry during the entire collection period. Prevalence of undernutrition was highest at diagnosis and disappeared after six months. Interestingly none of the patients treated for solid cancer was classified as obese. However, statistical comparison of the observed frequencies of malnutrition assessed by arm anthropometry in this study against the prevalence of malnutrition for the UK population was not possible because there are no expected frequencies of malnutrition obtained based on these measurements.

It can be assumed that solid cancer and its treatments cause FM depletion but not muscle mass depletion, especially at diagnosis. Therefore, this suggests a negative energy status existing from pre-diagnosis. These findings are in line with the published literature which indicates an increased REE in relation to tumour burden and a normalising effect of cancer therapy (den Broeder et al. 2001; Schmid et al. 2005; Stallings et al. 1989; Vaisman et al. 1993). Moreover, it could also be postulated that the depleted fat stores may be a reflection of anorexia and resultant decreased energy intake caused by the acute phase response (Falconer et al. 1994; Staal-van den et al. 1995). The replenishment of the fat stores after diagnosis suggests a positive energy balance, which could be attributable to the successful nutritional management of the patients, and the decreased tumour burden in response to chemotherapy, as observed elsewhere (den Broeder et al. 2001; Schmid et al. 2005; Stallings et al. 1989; Vaisman et al. 1993). Although not significant the increased BMI in response to NS observed in this study would suggest a pivotal role of nutritional management during cancer therapy in children with solid tumours.

The present study showed that patients with haematological cancers experience a rapid increase in FM during the first few months of treatments. This rapid and dynamic FM gain is an important finding when considered he fact that none of the patients was obese at diagnosis and 65% became obese by six months. This study had the major limitation of small sample size which reduced as the data collection was carried out. This is likely to have an impact on the results, and affected the

percentages of malnutrition observed, especially after the six month measurements. However, the results show a trend toward excess fat gain during the first six months treatment for leukaemia, which should not be underestimated, especially considering the increased risk in this group for the late onset for obesity (Nichol et al. 1998; Reilly et al. 1998; Reilly 2009; Ventham and Reilly 1999).

An uninvestigated dimension of ALL-increased risk of obesity is the effect of alternative phases on and off steroids during maintenance therapy, on body composition and the risk of late obesity. It is known that subjects who experience large FM losses tend to compensate with hyperphagia, with a consequent excess of body weight regain (weight over-shooting) (Dulloo et al. 2012). It could be argued that the alternating phases of low energy intake when off steroids and high energy intake when on steroids (Jansen et al. 2009) may cause FM losses during the off steroids period, followed by excess fat accumulation in response to hyperphagia during the steroid period. This could cause overshooting of the FM set point. Although, this study showed an increased in FM and weight gain, it is unknown if the patients studied returned to their pre-illness set-point FM or if they exceeded it. Future studies should aim to assess FM before ALL treatments and prospective measured body composition according to treatments phases.

When the cohort was stratified according to gender no differences in arm muscle area and arm fat area were observed between boys and girls, showing that there is no gender-associated risk of malnutrition.

In this study, BIA measurements were converted to FM% to standardise the results for age and gender and to allow statistical analysis. The studies (Delbecque-Boussard et al. 1997) carried out to assess longitudinal changes in children treated for cancer, presented the data as mean TBW, FFM and FM for the entire cohort. However, this approach was not applicable to the current study. This is because the number of patients measured at each time point varied greatly, and presenting the data as changes in mean TBW, FFM, and FM, would have not reflected the changes in body composition but changes due to age and gender.

This study showed that FM% was significantly higher than standard values at all time points. The lack of association between the FM% measured by BIA, BMI centile, and FM% measured by arm anthropometry would suggest some methodological bias. These results indicate that BIA may not reflect body composition in children treated for cancer. It could be argued that arm anthropometry only provides information on localised fat deposit, and should not have been compared to total FM%. However, fat deposition in children is more evenly distributed than adults (Roche et al. 1981) suggesting that they should be positive correlated.

The BIA technique had several methodological limitations which are likely to have affected its ability to measure body composition in this cohort. Firstly, the use of BIA to assess nutritional status during cancer treatments depends on the extent of accuracy of the prediction equation. In the current study, the only available equation for the paediatric cancer cohort was used (Brennan and Thomas 1997). However this equation has a wide limit of agreement (mean 0.9, limit of agreement = -2.46 to 4.06) with the deuterium technique. This is likely to have introduced some inaccuracy. Moreover, in the current study the SF-BIA was used, which has been indicated to be accurate only when assessing patients with normal hydration (Gudivaka et al. 1999) but not when measuring subjects with altered hydration (Patel et al. 1996). Since paediatric cancer patients are likely to have altered hydration status caused by the treatments and the disease (Warner et al. 2004) the accuracy of the measurement using the SF- BIA could be questioned. Moreover, during the data collection some of the conditions recommended for BIA measurement could not be met (Kyle et al. 2004a). For example a fasting condition was not observed for clinical reasons. Moreover it was not always possible for the patient to void their bladder before the measurement. This is because they were in isolation or bed bound, or they refused to void their bladder before the test. In addition, the repeated measurement was not carried out at the same time of the day.

Furthermore, the adequacy of the standard used for comparison may be in question. In this study it was not possible to use a single set of reference data because the

difference age groups covered by standards available in the literature. For patients between zero to five years the Fomon (1982) standard was used, which has the major limitation of using only one subject. For subjects aged five years above, the Laurson et al. (2011) standard was adopted. However, this has the limitation of being obtained using skinfold thickness. Therefore, considering the current study findings, the use of BIA in children during cancer therapy may not be indicated.

Because of weight and body composition variation associated with tumour size and treatment, it is pivotal to understand the ability of other anthropometric methods to assess nutritional status in children with cancer. Thus, in the present study, the agreement between BMI and arm anthropometry measurements to classify undernutrition in children treated for cancer was assessed.

This investigation showed that MUAC and TSF identified more patients as undernourished than BMI at recruitment (24%, 29% and 16% respectively). Moreover, this increased prevalence was associated with a very poor limit of agreement between arm anthropometry measurements and BMI. These results suggest that arm anthropometry measurements are able to identify more undernourished patients that BMI centile alone. It is unlikely that the increased prevalence of undernutrition, measured by TSF and MUAC in this prospective study, is a consequence of false positives leading to higher observed undernutrition rates. This is because it has been shown that arm anthropometry correlates with FM% obtained from air displacement plethysmography in children undergoing cancer therapy (White et al. 2011) which is a reliable and valid technique to assess body composition in children (Fields et al. 2002). Therefore it could be advocated that in children with cancer, arm anthropometry is a better indicator of nutritional deprivation than BMI centile alone.

A unique aspect of the present study is that it has not solely examined the prevalence of undernutrition according to several anthropometric measurements, but also assessed the limit of agreement between measurements. This approach gives more robust evidence that percentage alone, since it takes into account the agreement between measurements and the agreement occurring by chance. However, although

the kappa statistic is widely used in measuring inter-analyst agreement, it is known that this test behaves poorly in small samples. (Sim and Wright March 2005). Future studies with a bigger sample size are needed to test the agreement on assessing undernutrition between BMI and arm anthropometry in this specific cohort. Of all the studies (Murphy et al. 2009; Nething et al. 2007; Oguz et al. 1999; Pietsch and Ford 2000; Smith et al. 1991; Smith et al. 1991) available in the literature aiming to compare the prevalence of undernutrition according to different anthropometric parameters, none had determined the limit of agreement between the measurements investigated. Therefore, although they all show an increased percentage of undernutrition when assessed by arm anthropometry, it is unknown if that occurred by chance.

The findings in the current study highlight the importance of anthropometric monitoring during childhood cancer treatments from diagnosis onwards. Although BMI has the limitation of not measuring body composition, it is still a very valuable tool to assess nutritional status and its changes during cancer therapy. The advantages of this method are its simplicity for performance and interpretation. However, the findings of this study also suggest that given the known masking effect of cancer and its treatment on nutritional status assessed by weight related measurements (Pietsch and Ford 2000; Smith et al. 1991), the use of BMI centile alone may leave some undernourished patients undetected. Therefore, TSF and MUAC measurements should become part of the nutritional assessment of children treated with cancer especially in those subjects where the tumour can have a masking effect on weight. Nutritional assessment is important in order to assess the prevalence of malnutrition during the different phases of treatment, but also to allow comparison from a baseline measurement. With this approach NS can be promptly initiated and the patients' response closely monitored.

4.4.3 Nutrition support

This prospective investigation showed that 58% of children in the study cohort required some type of NS at some point during their cancer treatments. The haematological group had a higher need for OCS (50%) compared to the solid group

(33 %). On the other hand, only 10% of the haematological group required the most advanced nutrition support available, compared to 62% of the solid tumour group. This indicates a greater extent of nutritional depletion in children treated for solid tumours. These results reflect the spectrum of diagnosis associated with greater risk of undernutrition in the literature (Betcher and Ablin 1993; Han-Markey 2000; Rickard et al. 1986).

However, due to the small sample size in this prospective study, it was not possible to identify specific types of cancer associated with a particularly high risk of undernutrition. Moreover, the limited sample size did not allow the analysis of the need for NS in relation to the stage of disease, which is a known risk factor for undernutrition (Rickard et al. 1983). Consideration of the extent of use of NS in relation to treatment modalities indicated that the highest NS usage was among children receiving chemotherapy, followed by those receiving chemotherapy and radiotherapy with surgery. The lowest usage appeared to be amongst children receiving chemotherapy and surgery. Therefore, these results suggest an increased risk of undernutrition in relation to some treatment modalities, in particular chemotherapy alone. However, the limited sample size in the current study did not allow the analysis of the extent of nutrition support in relation to specific cancer diagnosis, treatments protocols and regimens. Althought these results are likely to be a reflection of both the diagnosis it self and the treatment, the specific associations between aspects of the treatment and nutritional implications could not be identified.

In the present study BMI centiles increased from initiation to the end of NS, however the changes were not significant. When the cohort was analysed according to nutrition support modality, it was observed that BMI centiles in those patients treated with OCS were decreasing, whereas BMI centiles in those patients treated with ETF increased. However, these results were not statistically significant. This lack of significance is probably caused by the limited sample size in this study. These findings suggest the positive effect of NS on preventing further nutritional deprivation and on improving nutritional status. These conclusions are further supported by the decreased prevalence of undernutrition from recruitment to six

months. Therefore, even though the changes were not significant, the results should not be underestimated.

In this study children were prescribed OCS but they did not take them regularly. Therefore, the decreased BMI centile in patients in OCS observed in this study may be a reflection of the lack of compliance to the oral supplement, rather than the inefficacy of OCS on counteracting undernutrition. It is a well known issue that in children, compliance in consuming OCS is poor (Han-Markey 2000). Moreover, even though OCS is largely used in undernourished patients, its effectiveness in counteracting cancer-related undernutrition and its effect on outcome is still unclear. A study conducted in cystic fibrosis patients showed that OCS did not improve energy intake, but rather disrupted food consumption (Kalnins et al. 1996). However, new more palatable formulations have been designed since that study was published. Therefore, there is now the need for more research to assess the efficacy of OCS on counteracting undernutrition in this population using these new formulations.

As with other studies (den Broeder et al. 1998; den Broeder et al. 2000; Rickard et al. 1979; Smith et al. 1992), the current investigation demonstrated a positive effect of ETF on counteracting undernutrition in children undergoing cancer therapy. It could be argued that the observed improvement in nutritional status was a consequence of an overall clinical improvement rather than a consequence of NS. However, in the present study the patients on ETF were undergoing aggressive chemotherapy, and although the treatments may have reduced the cancer burden, chemotherapy caused severe side effects which would have had negative effect on nutritional status (Betcher and Ablin 1993).

In this study it was not possible to examine the changes in body composition in response to NS. Therefore, it was not possible to assess whether the increase in BMI centile observed was a consequence of an increase FM, FFM, or both. Although arm anthropometry and BIA measurements were taken regularly every three months, the initiation and the end of NS did not coincide with these measurements and for ethical reasons it was not possible to take extra measurements between time points. On the

other hand, calculation of BMI at initiation and the end of NS was possible because the weight and height were closely monitored by the dietitian and noted at NS initiation and end.

The literature is lacking in studies aiming to assess body composition changes in response to NS during cancer treatment in children. A significant increase in skinfolds in response to nutrition support has been shown (Rickard et al. 1985), which demonstrates a positive effect of NS on replenishing body endogenous energy stores. However the authors did not assess whether, those changes were affecting FM and FFM equally. Therefore, research should now be addressed to understand the effect of NS on body composition with special consideration towards those patients who were obese at presentation or who became obese during childhood cancer therapy.

In summary, this study has identified some specific cancer types that had an increased requirement for NS during cancer treatment. The increased need for advance nutrition therapy observed in the solid group highlights the high risk for nutritional depletion in this specific group. Further studies, with a sample size adequate to allow stratification of the patients according to cancer type, stage and treatment protocol are now essential. These will require a multi-centre and even a multi-country approach. However, these types of epidemiological studies are very expensive, lengthy and complex. Therefore, robust data are required prior this type of studies to inform on the sample size required to achieve a clinically meaningful result, and evaluate areas that need to be investigated. This will allow the understanding of the association between those variables and the need for the nutrition support, hence, the development of specific guidelines for the nutritional care of this group.

4.4.4 Energy Balance and macronutrient intake

A major concern in the treatment of childhood cancer is that patients may not meet their energy requirements to support growth and sustain the body's needs. Additionally, increased energy intake may lead to the excess body weight gain observed in childhood cancer survivors (Odame et al. 1994; Reilly 2009; Ventham

and Reilly 1999). It is pivotal for the nutritional care of a childhood cancer patient to identify the phases during treatment where there is a higher risk of energy imbalance.

As discussed in Section 1.3, undernutrition and the consequent impaired growth are a consequence of an imbalance of the energy balance equation, where energy expenditure exceeds energy intakes, and obesity is a consequence of energy intake exceeding requirements. Therefore, when investigating both undernutrition and overnutrition during treatment for childhood cancer, it is essential to take into consideration dietary energy intake, energy losses consequent to malabsorption, and the metabolic requirements. However, in the current study, the substrate losses (e.g. from stools) were not determined for a range of logistical reasons. This research approach would have been an excessive burden to the nursing staff, the families and the patients. Moreover it would have been too costly.

Although one of the study objectives was to assess physical activity every six months, the level of patients' physical activity in this cohort could not be assessed. This was for the reasons discussed in section 4.3.8. Many studies have been carried out using the same physical activity measuring technique, in both healthy children (Reilly et al. 2004) and children treated for cancer (Aznar et al. 2006; Jacob et al. 2007; Jansen et al. 2009; Sanford et al. 2008) without any compliance issues. The discrepancy with this current study may be explained by differences in treatment phase when the participants were recruited. Recruitment in the current study occurred in the early stages of treatment, were everything is frightening and painful for the child, whereas the studies above were either carried out in healthy subjects (Reilly et al. 2004) or during maintenance phase (Aznar et al. 2006; Jacob et al. 2007; Jansen et al. 2009; Sanford et al. 2008).

During the data collection period the use of alternative methods to assess physical activity was considered. However, the subjective methods available, both questionnaires and interviews, were believed to be inadequate to assess physical activity in this cohort. First of all, these two methods rely on the ability to recall physical activity, which may be influenced by the judgment of the reporter or interviewer (Sallis 1991). Secondly, energy expenditure is obtained using a

prediction equation developed using adult subjects; hence it may not apply to children (Sallis 1991). Therefore, it was concluded that these two methods were not accurate and they would not have provided a good measurement of PA in children.

The present study examined spontaneous intake and intake with nutrition support. In order to ensure consistent data was collected, dietary intake was measured by the 24h multiple pass recall dietary recall technique. The method of choice to assess macronutrients intake in this study was the three day diet diary. This method has been shown to provide a relatively reproducible estimate of energy and macronutrients (Willett 1998). Although, it is subject to extent degree of error, provision of three days of data would have largely overcome the error resulting from memory lapses, making this error acceptable (Gibson 2005). However, immediately after the study was initiated; it became clear that this method of choice was too onerous for the family of this particular patient group. A consultation with the ward's dietitian confirmed that the families are too overwhelmed and they tend not to return the diaries. Moreover, similar issues with use of diet diaries in newly diagnosed pediatric cancer patients have been reported by other authors (Delbecque-Boussard et al. 1997; Poslusna et al. 2009; Sgarbieri et al. 1999). Therefore, it was decided to use the 24h multiple pass recall (Guenther et al. 1994). A similar dietary assessing method, the 24h dietary recall has been previously used in other paediatric cancer studies (Delbecque-Boussard et al. 1997; Poslusna et al. 2009; Sgarbieri et al. 1999)

The literature lacks studies aiming to assess the accuracy of dietary intake assessment methods in children treated for cancer. Therefore, to date there is no a valid dietary assessment method to estimate intake in this particular cohort, and the extent of error in estimating energy and macronutrients intake is unknown.

The 24h multiple pass recall was developed in the US with the aim of reducing the underreporting issue found with the standard 24h dietary recall technique (Guenther et al. 1994). However, the use of the 24h multiple pass recall outside the US, and particularly in children, is very limited. A study (Reilly et al. 2001) carried out in 3-4 year olds, showed that the 24h multiple pass recall was well tolerated by the families as very quick to be completed. However, regardless of this advantage, the dietary

assessment method was found to overestimate energy intake by 11%. The authors suggest that the bias may have been caused by the estimation of portion sizes. These results are of particular importance when interpreting the results in the current study.

However, despite the limitations of methodologies used to determine energy and macronutrient intake, the current study provided useful information on changes in nutrient intake during cancer therapy, and the results should not be underestimated. The current investigation demonstrated that, overall, childhood cancer patients met their daily energy requirements both *ad libitum* and with nutrition support, during the entire data collection period. However although not statistically significant, intakes both *ad libitum* and with nutrition support were lower than requirements at three months. Moreover, if the overestimation caused by the 24h multiple pass recall is taken into consideration; it is likely that actual dietary intake was even lower than quantified in this study. Additionally, when the patients were stratified according to diagnostic group, it was evident that the daily energy intake during the entire data collection period was different between the two diagnostic groups, with some time points being at increased risk of low or high energy daily intake such as diagnosis and three months.

Although the cohort was meeting their daily energy requirements overall, many patients were found to have intakes below 80% of individual requirements (Henry 2005). It should be highlighted that even though not significant, the reduced energy intake, if cumulative, may result in a prolonged energy imbalance which can lead to depletion of energy reserves impact on growth. The highest percentage of patients not meeting their energy requirements including those in NS, were observed at three months (40%), followed by nine months (20%), which was also the time with the highest observed incidence of undernutrition (section 4.4.2).

When the patients were stratified according to diagnosis, it was observed that the average daily energy intake both *ad libitum* and with NS for the haematological group at recruitment was much higher (163%) than the individual daily energy requirements. However, at three months, the daily energy intake was 57% and 62% of the individual energy requirements *ad libitum* and with NS respectively. Daily

energy requirements were not met by 30% and 80% of *ad libitum* and NS patients, respectively. Energy daily intake met the daily energy requirements thereafter.

The reasons for the dramatic energy intake fluctuations in the patients treated for ALL in the present study may be explained by the treatments with steroids as part of the protocol for ALL. This increases energy intake and causes steroid cushingoid appearance (Loprinzi 1995). In the first phase of treatment, ALL patients are treated with daily high doses of steroids to induce remission. After remission is achieved, a course of steroids is given for a week every month. In the induction of remission phase, the steroids are likely to increase appetite and minimise the emesis and nausea caused by chemotherapy. However, during remission phase, where the patients are still treated with aggressive chemotherapy, the effect on appetite and nausea of the steroids therapy is transient, during the week of treatments, but for the rest of the time this group of patients can experience the same side effects as their solid tumour counterparts. Therefore, they are likely to experience phases of excessive intake when on steroids, followed by a reduced intake for the rest of the month (Jansen et al. 2009). Since the data collection in this study was based on time intervals (three months) more than events (chemotherapy protocol phases), many patients were assessed during the off-steroid period. Even though an attempt was made to record whether they were on- or off- steroids, data analysis taking into account this variable was not possible due to the limited number of patients in this cohort.

On the other hand, median daily energy intakes both *ad libitum* and with NS in the solid group were above 100% of the energy requirements at each time point. However, at three months and six months 10% and 18% of the patients in the solid group where still not meeting their requirements (as >80% of individual requirements) even with NS. This is important in relation to the fact that this patient group had the highest prevalence of undernutrition at recruitment. Therefore, energy intake should not only meet the requirements but exceed them, to allow replenishment of their endogenous energy reserves, and to minimise wasting and sustain growth.

When the cohort was stratified according to gender, it appeared that although not significant, male patients had a reduced intake *ad libitum* (63%) compared to their requirements at three months. However, their intakes met the energy requirement when the NS was accounted for (89%). On the other hand, the female group had an adequate energy intake overall at each time point. It is not clear if there is a specific increased risk for reduced daily energy intake among male patients, or if the higher proportion of male patients and the small number of subjects used in this study biased the differences in energy intakes observed.

This study showed an increased overall energy intake from diagnosis to three months in the solid group, which was associated with an overall increase in BMI centile. Although the group was meeting the requirements as a whole, 17 % of the patients were still below the 80% of their daily energy requirements. These results further underline the increased risk of undernutrition among specific diagnosis groups, such those with advanced stage and unfavourable biology (Rickard et al. 1983). It also indicated the need for a large cohort size when investigating the nutritional risks for children treated for cancer, to allow stratification according to specific diagnosis, rather than the generic solid vs. haematological groups used here.

In contrast, whilst daily energy intake was reduced at three months in the haematological group, BMI centiles and FM were at their peak. It could be argued that a decreased daily energy intake in this specific childhood cancer group is essential to allow depletion of excess fat stores accumulated during the first phase of treatments. However, many aspects must be considered in the nutritional management of children treated for ALL. For example, obtaining adequate micronutrients from a low energy diet can be very challenging. This becomes even more complex if the overall dietary quality is affected due to the emotional stress of the family, the fear that the child is experiencing, chemotherapy's side effects, and the perception that the child is not eating enough. As a response, favourite foods, frequently those high in fat and energy, but poor in micronutrients, are consumed and those less favoured (e.g. vegetables), which are rich in micronutrients, are omitted. However, presently there is an absence of guidelines for the management of

obesity in children treated for cancer. Moreover the typical dietary advice given by the dietitian when a patients has a decreased energy intake and weight loss (regardless of actual BMI), in both solid and haematological cancers, is to increase the intake of energy dense food. This approach aims to increase the energy density of the diet in order to prevent nutritional deprivation (Alexander et al. 1997). However, this may not always be appropriate. Considering the increased risk for the late onset obesity in ALL survivors (Ventham and Reilly 1999), the reported increased mortality rate and increased risk of relapse among obese children during cancer therapy (Butturini et al. 2007; Lange et al. 2005) there is now evidence to support the need for specific nutritional strategies aiming to address obesity in this particular cohort.

The overall reduced daily energy intake *ad libitum* observed in this study is in agreement with other studies (Bond et al. 1992; Carter et al. 1983b; Delbecque-Boussard et al. 1997; Smith et al. 1991), and it has been reported to be one of the main contributing factors to the development of undernutrition during childhood cancer therapy (den Broeder et al. 1998). However, comparison of the energy intakes observed in this study to the published literature is problematic due to the different methodologies used to assess nutrient and energy intake, the different phases of the disease studied, and the different diagnosis included in the studies. Delbecque-Boussard et al. (1997) observed a significantly lower energy intake at diagnosis in ALL patients. However this difference disappeared by day thirty-six. Similarly, the current study observed a reduced intake in the ALL group, not at diagnosis, but at three months. Moreover, the current study identified only a small percentage (8%) of patients failing to achieve their daily energy requirements *at libitum* at diagnosis compared to Smith et al. (1991), who observed that 27% of the total cohort treated for various types of cancer failed to achieve requirements. However, when stratified according to diagnostic group, 30% of the solid tumour patients in this study did not meet their requirements *ad libitum*.

This discrepancy between the results may be justified by many factors such as the different sample sizes, the type of diagnosis included in the study, the different time

frame and the estimate energy requirements used to compare intakes against. For example, Smith et al (1991) had a greater proportion of patients with solid tumours (excluding benign brain tumours) than the current investigation (68% vs. 50%) and a bigger sample size, which may have affected the results. Moreover, the baseline measurement in the current study was carried out between one and two weeks from diagnosis, as advised by the haematology-oncology team. Consequently, the patients were already undergoing chemotherapy when measured at baseline. In contrast Smith et al (1991) assessed dietary intake retrospectively based on recall of food eaten immediately prior to diagnosis. Moreover, in Delbecque-Boussard et al. (1997) took measurements before any treatment was started. This suggests that the discrepancy in the baseline results could be explained by the fact that many patients in the current study were taking steroids at the time of assessment. Moreover, Delbecque-Boussard et al. (1997) stopped assessing intake after less than three months, and Smith et al (1991) assessed dietary intake before diagnosis only, so energy intake after three months of therapy is unknown and comparison to current results is impossible.

Another important factor that needs to be considered when interpreting the daily energy intake data is the standard used for comparison. In this study, the energy requirements were determined using the Henry equation (2005) adjusted for physical activity, as explained in the section 4.2.9. Since physical activity is the most variable component of total energy expenditure, it has to be accounted for when assessing daily energy requirements. Specific physical activity could not be measured for this cohort. Therefore, based on the published evidence supporting a decreased level of physical activity during treatments for childhood cancer (Aznar et al. 2006; Jacob et al. 2007; Jansen et al. 2009; Sanford et al. 2008), the physical activity level for lesser physical activity levels was used for the calculation of the individual energy requirements. However, it is not clear whether this estimation of the level of physical activity accurately reflects this population.

A variety of prediction equations are described in the literature to calculate BMR (Henry 2005; Schofield et al. 1985) and the studies available (Bond et al. 1992;

Carter et al. 1983b; Delbecque-Boussard et al. 1997; Smith et al. 1991) investigating daily energy intake used a variety of different equations, which may have caused some discrepancies between their results. Moreover, irrespective of which equation was used to assess daily energy requirement, all these equations are developed for healthy groups and their use in disease can cause substantial error (Elia 1992b; Henry 2005; SACN 2011). This is because the hypermetabolic effect of the disease and the hypometabolic effect of decreased body weight and lean body mass alter BMR, even when weight, gender and height are taken into consideration (Elia 1992b), although the extent of this is unknown.

Although some authors has observed an increased REE depending on tumour burden at diagnosis (den Broeder et al. 2001; Schmid et al. 2005; Stallings et al. 1989; Vaisman et al. 1993), the evidence to support a long term hyper-metabolism in children remains inconclusive (Green et al. 2008). In the clinical dietetic management of adult cancer patients, a stress factor is added to BMR to account for the metabolic demands of the cancer (Barak et al. 2002; Delarue et al. 1990). On the contrary, this stress factor is not added to pediatric cancer patients, probably due to the limited evidence on REE and the consequent lack of specific stress factors for use with paediatric cases. It is unknown whether the patients in this current study were hypermetabolic. Therefore it is unknown whether the predicted individual energy requirements calculated using the Henry (2005) equation for healthy children represent an acceptable estimate for the children studies in this research. Further work which examines the REE in childhood cancer patients is now essential and this should take into consideration the different protocols and treatment phases of childhood cancer. Only then clinically effective assessment of energy intake adequacy can be carried out.

Adequacy of energy intake was based on <80% of the daily energy requirements which has been largely used by others (Carter et al. 1983a; Smith et al. 1991). However, its ability to detect energy intake adequacy in children with cancer has not been validated. Moreover, when assessing energy requirements in a disease state is essential not only to consider the requirements to maintain energy balance, but also

the energy required to allow changes in body composition. This is pivotal to allow repletion of endogenous stores in undernourished patients and depletion of excess FM in overnourished patients.

An important finding of this study is that all the patients at each time point, regardless of their diagnostic group, were meeting their protein requirements. These results show that protein energy undernutrition in this cohort is uncommon. Similar findings have been reported elsewhere (Carter et al. 1983, Delbecque-Boussard et al. 1997, Garcia et al. 1989). However, in this study and previous studies (Carter et al. 1983, Delbecque-Boussard et al. 1997, Garcia et al. 1989) the protein intake was compared to the DRV for the healthy children. This criterion to assess adequacy may be questionable since the specific protein requirement for children treated for cancer is unknown. An example where protein requirements for a healthy child might not apply to this population group is in the temporary increase in energy and protein requirements following a period of infection and slow growth, to allow catch up growth (MacDonald 2007). Extra protein is required to allow replenishment of lean tissue as a consequence of starvation and a catabolic state. The amount of protein needed to allow catch up growth varies according to the rate at which catch up growth is achieved, and the weight of the child. It has been suggested that the protein requirements can be up to 70% greater than those based on actual weight and age (FAO 2010).

Additionally, in this study the biological value of the protein consumed was not assessed. The dietary requirements used in this study (Department of Health 1991), are based on estimate of the amount of high-quality egg or milk protein required for nitrogen balance. However, considering the high amount of protein foods consumed and the type of food eaten, it is likely that diet provided high biological value protein.

The recommendation for fat intake in healthy children in the UK is a gradual transition (commencing at two years) from the high fat diet of infancy (around 35%) to a modified diet by five years providing <35% energy from fat (Department of Health 1991; Department of Health Report on Health and Social Subjects 1994). The

current investigation may indicate that, although not significant many patients were consuming a high fat diet during the treatments especially at three months.

The findings of this study are probably a reflection of the dietetic recommendation for an energy-dense diet during treatment for cancer (Alexander et al. 1997). The recommended high fat diet aims to prevent waste and restore endogenous energy stores in those patients experiencing decreased intake. However, the increased risk of late onset of obesity in ALL patients (Ventham and Reilly 1999), and the increase in FM percentage observed in this current study, casts doubt on this dietetic practice in ALL patients. Additionally, it highlights the importance of specific guidelines for childhood cancer patients who are obese at presentation or at high risk of treatment related obesity. Moreover, during childhood, eating behaviours are developed which set the foundations for future eating habits and weight status (Savage et al. 2007). Therefore, the encouragement of a high fat diet for a prolonged period of time, in patients that are already obese may have detrimental effects later in life. This may negatively influence food choice and eating behaviours as adults.

This study showed that many patients only achieved their daily energy requirements through NS. The discrepancy between daily energy intake *at libitum* and the intakes with NS serves to highlight the importance of nutrition intervention to achieve daily energy requirements. This study showed that patients in this cohort may have suboptimal intake during treatment if not provided with NS. This can lead to undernutrition and, in turn can impair growth. However, a number of patients receiving NS in this cohort were not meeting their energy requirements even with NS. This discrepancy between intake with NS and the daily energy requirements highlights the difficulties of tolerating enteral feeding during cancer therapy for some patients (den Broeder et al. 1998). Although, chemotherapy treatments share the same side effects as nasogastric feeding, it is reasonable to assume that the low tolerance for some patients to ETF was a consequence of the side effects of chemotherapy treatments, such as nausea, diarrhoea and vomiting. While the current study did not aim to assess the impact of chemotherapy side effects, the dietetic notes and consultation with the oncology dietitian showed that the lowest tolerance

to ETF occurred during chemotherapy and improved after the completion of the chemotherapy course. Therefore, although anecdotal, these observations illustrate how energy intake in this patient group is affected by the treatments phase even when NS is delivered via ETF.

In summary, children treated for cancer are likely to experience a reduced energy intake during the first three months of treatments, with the exception of ALL patients who have a high energy intake in the first month of treatment. This study has shown that energy provided by NS is essential for some patients to achieve their daily energy requirements, even though tolerance of the feeds can be problematic during the cycles of intense chemotherapy. Currently, the mechanisms involved in weight and FM gain observed in ALL patients are not fully understood. Further studies that focus on the nutritional management of this specific patient group are now pivotal.

4.4.5 Biochemical profile

Cancer and its treatment cause many metabolic disturbances which can lead to intricate metabolic abnormalities in the host. Many cancer treatments are mediated by a free radical dependent mechanism (Sangeetha et al. 1990) which is likely to affect micronutrient status. Moreover some prescription drugs may interfere with nutritional status by altering absorption, excretion and metabolism of nutrients (Force et al. 2003; Valuck and Ruscin 2004; Gibson 2005). Therefore, cancer and its therapy may cause alterations in mineral and vitamin status. The present study longitudinally examined the micronutrient status of children to detect clinical or subclinical deficiency states by blood assessment. The choice of micronutrients investigated in this study was based on the biochemical tests currently available at the RHSC. The plasma level of the micronutrients investigated should generally reflect the body content of the nutrient examined. However, plasma levels may be affected by biological factors such as inflammation, chemotherapy, and the disease, and thus may not accurately reflect nutritional status (Gibson 2005). Therefore, in this study the entire clinical profile of the patients was taken into consideration when interpreting the results.

The liver test function showed a damaging effect of treatment on the liver, whereas renal function was not affected at the time points when data were collected. A full discussion of the detrimental effect of chemotherapy on the liver and the kidneys goes beyond the purpose of this thesis. However, in order to interpret the results it is essential to take into consideration the functionality of these metabolic organs.

In this study, albumin was borderline low in 20% of the total cohort at diagnosis. When albumin was analysed in relation to hsCRP, it was shown that it was associated with inflammation. Although albumin has been largely used as indicator of nutritional status in childhood cancer studies (Kibirige et al. 1987; Yu et al. 1994), its use to detect poor nutritional status is believed to be inappropriate (Donaldson et al. 1981; Forse and Shizgal 1980; Merritt et al. 1985; Santos et al. 2003). This is because albumin is an acute phase reactant, and hypoalbuminemia is caused by inflammation as a sparing mechanism to sustain the synthesis of inflammatory chemicals needed to maintain the inflammatory response (Donaldson et al. 1981; Forse and Shizgal 1980; Merritt et al. 1985; Santos et al. 2003). Therefore, it is likely that the low plasma albumin observed in this study is an indicator of inflammation rather than undernutrition.

In the current study, vitamin B_{12} was found to be low in a small percentage of patients during the entire data collection period, with both solid and haematological cancers being equally affected. Quantitative comparison of the prevalence of vitamin B_{12} deficiency to the NDNS (Department of Health 2012) was not possible due to limited patient numbers in this study and the different age group covered by the NDNS (Department of Health 2012). Therefore, it is not possible to establish if the vitamin B_{12} deficiency observed in this study reflects the healthy population or if it is caused by metabolic abnormalities during cancer therapy. Moreover, the literature is lacking in studies of vitamin B_{12} status in children during cancer therapy.

The commonest cause of vitamin B_{12} deficiency is the lack of intrinsic factor produced by the stomach, which causes impaired absorption (Department of Health 1991). However, in this study the lack of intrinsic factor as a leading cause of vitamin B_{12} deficiency seems unlikely, considering that the deficiency resolved

without any intervention in all the patients. A possible explanation for the transient vitamin B_{12} deficiency observed in some patients in this study could be the use of proton pump inhibitors (PPI). These drugs are often prescribed during cancer therapy in patients taking steroids, and to treat excess gastric acid production as consequence of the chemotherapy treatments. The presence of gastric acid is needed for the association of vitamin B_{12}, with intrinsic factor required for the absorption in the ileum.

Many studies (Force et al. 2003; Valuck and Ruscin 2004) have identified an association between the use of PPI with low vitamin B_{12} and pernicious anaemia, with long term users being at higher risk. Although only a small percentage of patients in this cohort were found to be vitamin B_{12} deficient, monitoring of vitamin B_{12} status for those on long term PPI courses may be recommended. This is especially relevant considering the role of vitamin B_{12} in blood cell formation and maintenance of brain and nervous system function (Department of Health 1991). Moreover, pernicious anaemia is detected by measuring haemoglobin plasma concentration, which in this group is generally low due the chemotherapy. Therefore, blood monitoring of vitamin B_{12} is the best method to detect deficiency. For those patients who required supplementation, the only option for administration may be the parenteral route. This is because many of these patients are thrombocytopenic and intra muscular injections can cause significant muscle haematomas as a result. Overall, the current findings highlight the risk of vitamin B_{12} deficiency for those patients treated for long term with PPI. In response to this finding, children treated for cancer at the RHSC are now monitored for vitamin B_{12} status.

Along with vitamin B_{12}, folate has an essential role in cell division and growth. Plasma folate has been reported to be a good indication of folate status (Department of Health 1991) and this assessment technique has recently been introduced in the NDNS to assess folate status (Department of Health 2012). In the current study, folate deficiency was only found in one patient. Therefore, poor folate status in childhood cancer seems to be unlikely. However methotrexate is known to cause folate deficiency through inhibition of dihydrofolate reductase (Manna et al. 2005).

Consequently children treated with methotrexate may be at risk of poor folate status. However the literature lacks studies aiming to evaluate the folate status of children with cancer, and comparison to the literature was not possible. Moreover it may be possible that folic acid supplementation may interact with the chemotherapy. Only one study aimed to investigate this topic (Lennard et al. 1986) and it showed that folate supplementation may interfere with the treatments. However, the study is very dated and further work which examines folate status in children during cancer therapy and the role of supplementation is required.

In this study, vitamin E status was assessed using serum α−tocopherol: cholesterol ratio. Alpha-tocopherol is the predominant form in human tissues, and levels of circulating α−tocopherol are correlated with circulating lipids (Horwitt et al. 1972). To account for the different plasma lipid levels, plasma tocopherols can be expressed as a ratio with plasma total cholesterol. This study showed that all the patients had a normal α−tocopherol: cholesterol ratio at any time point. These results are in contrast with Malvy et al. (1997) who concluded that children treated for cancer have low vitamin E status compared to their matched healthy counterparts. However, in their study, the plasma α−tocopherol was decreased in the cancer patients, whereas the α−tocopherol: cholesterol ratio did not differ from the controls. Therefore, it could be postulated that discrepancy in the results was caused by the different assessment method. It appears that when measured by the recommended parameter of α−tocopherol: cholesterol ratio (Horwitt et al. 1972), vitamin E status is not affected. However, vitamin E status in children with cancer has not been extensively assessed and the limited sample size in this study does not allow the drawing of any conclusions. Therefore, this topic requires further elucidation.

4.4.6 Vitamin D, PTH and calcium axis

This study aimed to compare vitamin D status, plasma calcium, plasma phosphate and parathyroid function in children treated for cancer. This showed a high prevalence of low serum 25(OH) D during the data collection period. It must be noted that when patients were diagnosed with poor vitamin D status, vitamin D supplementation was started. Considering the time for blood results to be analysed

and interpreted, and the time necessary to initiate the intervention, it is likely that the results from the six month measurements onwards have been affected by this intervention.

In healthy populations, plasma 25(OH) D concentrations show a marked seasonal variation, being lowest during winter and highest during summer (Lund and Sørensen 1979). In the UK, the population relies on body stores and dietary vitamin D to maintain vitamin D status during winter months (SACN/RCPCH 2007). Interestingly, this study did not indicate any seasonal differences in plasma vitamin D. These results support the idea that children treated for cancer do not spend adequate time outdoor to allow vitamin D synthesis. Therefore, it highlights the inability of the child to replenish their vitamin D stores during the summer months and the importance of dietary sources to meet vitamin D requirements in this cohort.

The median plasma level of vitamin D in this study cohort was generally lower that that reported by the NDNS (Department of Health 2012) for a comparable age group (11-18 years of age). The prevalence of vitamin D deficiency was found to be higher in the solid tumour group at diagnosis compared to the haematological group, with 44% of the solid tumour patients being vitamin D deficient compared to the 29% of the haematological patients. However, at three months the haematological group (33%) had the highest prevalence of vitamin D deficiency compared the solid group (0%). Low plasma 25(OH) D was associated with low plasma calcium, and in some patients, with low plasma phosphate. The lack of association between calcium and vitamin D is due to the tight regulatory mechanisms that control calcium homeostasis, preventing plasma calcium increasing above a maximum concentration at higher plasma 25(OH) D.

Statistical comparison against the NDNS prevalence of vitamin D deficiency (Department of Health 2012) was not performed because of the different age group covered by the survey. However, quantitative comparison, showed a clear increased prevalence of vitamin D deficiency in this cohort compared to the 19.3% reported by the NDNS. Indeed this inconsistency may be explained by the latitude differences between Scotland and the entire UK. However, this observation may also suggest a

particularly high risk for vitamin D deficiency in childhood cancer patients as previously reported (Helou et al. 2008; Sinha et al. 2010; Halton et al. 1996). However, comparison to the prevalence of vitamin D deficiency reported in the literature is difficult because of the different diagnostic groups covered in the literature.

As discussed, it is plausible that childhood cancer patients do not spend much time outdoors, even before diagnosis, due to the disease and the side effects of treatments. Moreover it is unlikely that the diet adequately compensates for the luck of sun exposure, considering the limited sources of dietary vitamin D (SACN 2007) and the poor nutritional status during cancer therapy.

The increased prevalence of poor vitamin D status observed in the haematological patients after treatment was started highlights the possible detrimental effects of steroid therapy on vitamin D status (Zhou et al. 2006). This would put this group of patients at even higher risk of vitamin D deficiency than their solid tumour counterparts. Moreover, Vitamin D in obese subjects is deposited in fat (Mawer et al. 1972) and it has been recently suggested that vitamin D status negatively correlates with BMI in adults and adolescents. In this study, BMI and vitamin D status were observed to have an '∩' shaped association with both low and high BMI being related to poor vitamin D status. Hence the trend towards obesity during cancer therapy observed in ALL patients may be an independent risk factor of vitamin D deficiency (Baradaran et al. 2012; Goshayeshi et al. 2012; Zwart et al. 2011). In contrast, the association with low BMI would suggest a general detrimental effect of poor nutritional status on vitamin D status. This is likely to be related to decreased nutrient intake, disease severity and the consequent lack of sunshine exposure.

Vitamin D deficiency is associated with secondary hyperparathyroidism. A negative association between plasma PTH and plasma 25(OH) D has been extensively reported (Chapuy et al. 1997; Ooms et al. 1995). Similarly, some authors have reported hypoparathyroidism to be associated with low plasma 25(OH) D (Sahota et al. 2001). This finding suggests that in some patients, the normal compensatory mechanism to maintain calcium homeostasis did not occur. Low plasma vitamin D

causes reduced calcium absorption, which leads to reduced plasma calcium. This, in turn, causes the release of parathyroid hormone which restores 1, 25(OH) D levels and enhances the release for calcium from the bones. In the current study, it appeared that some patients did not have an adequate PTH response. This failure of the parathyroid gland to support the adequate PTH response has been observed elsewhere in adult female subjects (Sahota et al. 2001). The authors suggested that this is caused by decreased plasma magnesium (Sahota et al. 2001). However, in the current study, plasma magnesium was within normal levels hence, the causes for failure of the parathyroid to support the adequate PTH response in this study are unknown.

These findings clearly suggest the need for screening and potential supplementation of vitamin D. Based on this study's results, the Royal Hospital of Sick Children, in collaboration with the author, has developed a protocol for vitamin D screening and supplementation during cancer therapy. All patients admitted with a cancer diagnosis are now started on a calciferol supplementation regime at a dosage to treat insufficiency and their plasma 25(OH) D is measured. Once the results from the screening are ready, the calciferol dose is adjusted as shown in Table 4.14 and plasma 25(OH) D monitored. This strategy was based on the length of time required for the blood tests to be analysed and the need for a prompt intervention.

	< 6 months of age	**> 6 months of age**	**> 1 year of age**
Insufficient	200-400 IU/d	200-400 IU/d	400-800 IU/d
Deficient	3000 IU/d for 8-12 weeks	6000 IU/d for 8-12 weeks	6000 IU/d for 8-12 weeks

Table 4.14 Treatment of vitamin D deficiency and insufficiency according to age (Pearce and Cheetham 2010)

However, the efficacy of vitamin D supplementation to improve vitamin D status in children treated for cancer has not been proven yet. Therefore intervention studies should aim to elucidate this topic, especially in obese patients or those taking steroids. It had been observed that pharmacological doses of 6000 IU/d given for a prolonged period of time lead to increased plasma 25(OH) D accompanied with

hypercalcemia. Vitamin D toxicity occurs at plasma 25(OH) D > 200nmol/l (Gertner and Domenech 1977; Mawer et al. 1985; Rizzoli et al. 1994). Therefore considering the risk of toxicity, it is important to monitor plasma 25(OH) D during supplementation and to establish if the current recommendation for healthy children applies to this cohort. This is extremely important considering the unknown interaction of chemotherapy on nutrient metabolism.

4.4.7 Serum vitamin A, supplementation and toxicity.

The present study has shown that 25% of haematological patients had low plasma retinol at three months. Although the cohort was small, these results may suggest either an increased demand for the vitamin or a decreased dietary intake during cancer. However, from the limited data available in this study it is not clear if the increased risk observed in the haematological occurred by chance or if this particular patient group it is at higher risk. Other studies (Malvy et al. 1997) have reported low plasma retinol in childhood cancer patients affected by different diagnosis suggesting that vitamin A deficiency is common among all diagnosis.

An interesting finding of this study is the excess plasma retinol observed in several patients during treatments, with two patients being above toxicity level. In this study blood was taken when it was convenient for the nursing staff and generally not in a fasting state. Therefore, it is likely that the observed plasma vitamin A above the normal range, but below toxicity, was caused by the postprandial transient increase in plasma vitamin A.

During the data collection period, four patients were supplemented with a multivitamin solution for children (ABDEC, Parke-Davis/Pfizer) containing retinol as vitamin A palmitate 733 mg/ day for children and 362.5 mg/d for babies. The reasons for supplementation varied, from poor vitamin D status, to parental concern about vitamin intake. The two patients found to have toxicity level plasma retinol had normal or elevated plasma retinol at initiation, and after taking the supplements, reached toxicity level within three months. The reasons for plasma retinol toxicity at safe levels of vitamin A supplementation are unknown. It has been suggested that it may be caused by decreased hepatic uptake (Smith and Goodman 1976). These

results may imply that the liver damage caused by chemotherapy affects vitamin A metabolism in children during cancer therapy. Although the number of patients was very small, and conclusions can not been drawn based on only two patients, these results are important, and they call into question the safety of vitamin A supplementation in this cohort. Moreover they stress the importance of micronutrient status monitoring during cancer therapy. It has to be noted that in consideration of the current findings, vitamin D supplementation at the RHSC is now given as vitamin D alone and not as a multivitamin complex.

4.4.8 C- reactive proteins, copper, zinc, selenium and ferritin

Research in the area of trace elements and minerals status in children treated for cancer has previously focused on plasma zinc and copper concentrations (Carpentieri et al. 1986; Cavdar et al. 1980; Gupta et al. 1994; Malvy et al. 1997; Mocchegiani et al. 1994; Sgarbieri et al. 1999).

Similar to the studies above, this study showed increased plasma copper and decreased plasma zinc. However, the current study is the only study to analyse copper and zinc in relation to inflammation. Although hsCRP values were missing for some patients, a link was observed between inflammation and abnormal level of copper and zinc. Zinc and copper are acute phase reactants, and the changes in plasma concentration are likely to be caused by inflammation rather than undernutrition (Galloway et al. 2000). This is further supported by the normalising effect of chemotherapy and end of treatments on zinc and copper plasma levels observed during the data collection. Moreover, in this study few patients were identified as selenium deficient by the blood test, and patients were reported to have extremely high level of ferritin, which was associated with inflammation. Similarly to copper and zinc, selenium and ferritin are acute phase reactants and their plasma levels during an acute phase do not assess selenium and iron status but inflammation. Therefore, plasma levels of these compounds should be use as indicators of poor nutritional status only when the patient does not have acute phase status. However, determination of poor nutritional status without biochemical indices but by physical examination can be challenging. This is because chemotherapy has a masking effect

on physical signs and symptoms of deficiency. For example alopecia is sign of biotin deficiency (Gibson 2005) but also a side effect of chemotherapy. Therefore, the assessment of micronutrient status in this cohort can be problematic.

The findings in this current study highlight the detrimental effects of cancer and its treatments on micronutrient status, and the importance of monitoring during childhood cancer treatments.

4.5 Conclusions

This research aimed to identify the risk factors for both under and over- nutrition in childhood cancer. These findings underlined the common risks of undernutrition and obesity in this childhood cancer cohort, and also indicated apparent differences in nutritional risk according to diagnosis and treatment. It is now apparent that nutritional screening during cancer therapy is urgently needed.

The initial aim was to define specific parameters such as age at diagnosis, cancer treatment, type of tumour and duration of illness (important in determining nutritional risk) using BMI centile as primary outcome. The particularly small number of newly diagnosed childhood cancer patients during the data collection period was a major limiting factor for the current study. This is a reflection of the low incidence of childhood cancer and the particular low incidence during the data collection period. The small sample size, and the many drop outs, has prevented statistical examination by unifactorial and multifactorial analysis for the identification of specific factors contributing to the development of under and overnutrition. Moreover, the small sample size, and the lack of statistical strength, may have led to type I and type II errors, leading concerns over the strength of the results.

However, although this study had the limitation of a small cohort size, it had the strength of following a group of patients for a long period during cancer treatments using several nutritional parameters. Hence, it still has achieved the study aim and objectives, providing important observational information on nutritional status during cancer treatments.

In summary, this study has shown that solid cancer patients have an increased risk for nutritional deprivation, low endogenous energy stores and increased requirement for nutrition support. In contrast, the haematological group experiences excess weight gain, excess endogenous fat storage and increased energy intake in the first phase of their treatments. Moreover, this current study has highlighted the importance of nutrition support during cancer therapy to achieve energy requirements, and its effectiveness in counteracting further nutritional depletion.

Finally, the findings in this current study have shown a detrimental effect of cancer and treatments on micronutrient status. This evidence supports the need for micronutrient monitoring in this patient group. Remarkably, the preliminary vitamin D and B_{12} findings have already led to the development of clinical guidelines for the routine monitoring of micronutrients at the RHSC, Edinburgh, further highlighting its importance. However, more research is needed to assess the safety of nutritional intervention in this patient group, as treatment may affect micronutrient metabolism.

It is apparent that extended longitudinal monitoring of nutritional status in children with cancer is now essential. Therefore, more research is now needed to identify the specific risk factors for malnutrition in paediatric cancer, such as age at diagnosis, gender, type of tumour, stage of tumour, treatment modalities, and protocols and stage of treatments. This research is still on-going and hopefully, by the end of the data collection period (January 2014) it will have achieved a sample size adequate to allow stratification according to these variables and more powerful statistical analysis.

It is anticipated that the findings from the full set of data will allow the development of a screening tool specifically designed for this cohort. This is intended to facilitate early and effective nutritional intervention to reduce the risk of nutritional problems in children with cancer throughout the course of the disease and its treatment.

5 CHAPTER FIVE
SUMMARY AND CONCLUSION

Despite considerable interest in the prevalence of malnutrition in childhood cancer patients and its impact on the outcome, little attention has been paid to their nutritional care. To date, there are no clinical guidelines for the nutritional management of this group of patients and the research is scarce and fragmented. Moreover, little is known about micronutrient status during childhood cancer therapy. Therefore, understanding the factors that contribute to the development of both undernutrition and obesity found in childhood cancer will prove central to the nutritional management and intervention of this patient group.

The current series of investigations in children with cancer have shown that this patient group has a particularly high risk of undernutrition throughout treatment and even in the remission phase. In the prospective study undernutrition was not a common feature after six months of data collection; however, it is likely that this reflects the small sample size rather than a low risk for undernutrition. Moreover, this current study has shown that obesity is also a common feature of childhood cancer during both the treatment and remission phases.

Stratification of childhood cancer patients by diagnostic group has highlighted differences in nutritional status, body composition, dietary intake and the need for NS. The prevalence of undernutrition has been observed to be higher than expected for the UK population at both diagnosis and during treatments for both solid and haematological groups. However, the two studies showed conflicting results for the prevalence of undernutrition at diagnosis for the haematological group. It could be postulated that this inconsistency originates from the small sample size of the prospective study. Moreover, it is likely that the retrospective study had included high nutritional risk haematological malignancies such as high risk ALL,I n contrast to this current study where all the ALL patients were low and standard risk ALL. Although undernutrition throughout the treatments and in the remission phase was

common in both solid tumour patients and haematological patients, obesity was higher than expected for the UK population in haematological patients only. It is apparent that undernutrition is a consequence of the metabolic disturbances caused by both cancer and treatments and it can reflect disease status. However, the causes for the onset of obesity in childhood cancer patients are still not fully understood.

The current studies showed a high need for NS during childhood cancer treatments. The extent of use of NS in relation to cancer diagnosis and treatment modalities has showed that that a high proportion of children receiving some type of NS, required the most advanced NS treatment from the early stages of therapy. This indicates a large extent of nutritional depletion. Although almost half of the children received at least one type of NS, the data showed that within both solid tumours and haematological malignancies, there are specific types of cancer which are associated with a particularly high risk of undernutrition. In particular, CML, AML, malignant bone tumours, Neuroblastoma and CNS malignancies required advanced NS.

Consideration of the extent of use of NS in relation to the treatment modalities indicated that the highest usage was among children receiving chemotherapy and radiotherapy (recurrence treatment). The lowest usage appeared to be amongst children receiving surgery only. These results suggest an increased risk of undernutrition in relation to some treatment modalities, in particular chemotherapy. However, it is not clear whether this is a reflection of the diagnosis itself, the treatment modality alone, the disease severity or, more likely, a combination of all factors. Moreover, chemotherapy comprises many different treatment protocols and therefore it was not possible to identify specific associations between aspects of the treatment and nutritional implications.

In some patients with solid malignancies, endogenous energy reserves were considerably depleted at diagnosis when compared to the reference values, suggesting an increased reliance on the provision of energy from fat to maintain energy balance prior to diagnosis and during the first phase of treatment. In contrast, haematological patients experience excess fat deposition during the first months of treatment suggesting a prolonged positive energy balance. Many clinicians and

authors consider weight gain to be a side effect of steroid therapy, however whilst this contribute to the early weight gain in haematological patients, it cannot be the solely cause for the long term increased risk for obesity observed in this current study and reported in the literature. A well known risk factor for the late onset of obesity with modern treatments is the reduced physical activity; however it seems unlikely that the reduced physical activity alone can account for the increased risk of obesity in this cohort. It may be speculated that there is an adaptive response caused by excess FM loss during chemotherapy, followed by excess fat storage during on-steroids periods, which may lead to fat overshooting and an early adiposity rebound. The understanding of the mechanisms causing excess body fat in this cohort is now pivotal to prevent this sequela.

Energy intakes were found to be lower than recommendations in those with solid tumours during the first phases of treatments. This reduced intake may in part account for the depletion in the energy stores observed in the solid group. In some patients, NS was essential to achieve the recommended daily energy intake. These observations, in conjunction with the effectiveness of NS in preventing further nutrition deterioration and improve nutritional status, highlight the importance of nutritional monitoring and NS in this cohort. However, despite receiving NS, many patients were still unable to meet the prescribed targets due to poor tolerance of the feeds, as a consequence of treatment side effects. In light of these findings, novel strategies aiming to detect nutritional risk early are required to initiate NS as soon as possible to prevent excessive nutritional deterioration.

In contrast, the haematological group was found to have an increased daily energy intake during the first phase of treatments, followed by a reduced daily energy intake. The observed increased energy intake is likely to have been a consequence of steroid therapy. The results of increased energy intake in conjunction with weight gain suggest a positive energy balance during the first phases of treatments, which is known to continue into remission. Although obesity is a well-known issue in ALL, there are no specific clinical guidelines to address this nutritional concern in this specific cohort. Nevertheless, the simple clinical guidelines for the management of

paediatric obesity were not adopted in this patient group during the study data collection. Interestingly, obese patients were advised to have an energy dense/high fat diet, which may be inappropriate. Additionally, the literature lacks intervention studies aiming to modify patients' behaviour or treatment regimens in order to prevent the late onset of obesity. Therefore the appropriate clinical management of excess weight gain in ALL is yet to be determined.

A particular strength of the present study design is that it permitted prospective examination of micronutrient status. It is apparent that cancer and its therapy cause metabolic abnormalities which may affect micronutrient status. This study has shown that children treated for childhood cancer are at high risk of vitamin D deficiency. Moreover, due to the impaired absorption caused by PPI, vitamin B12 deficiency can also occur. Perhaps more importantly, despite being supplemented with safe doses of vitamin A, few patients quickly reached plasma toxicity level. In view of these findings new strategies that aim to assess micronutrient status from diagnosis onwards are required. Moreover, multivitamin supplementation, a common practise in children with cancer, should only be advocated when a specific micronutrient deficiency is identified. This should be done under close supervision by the medical and dietetic staff along with blood screening to assess micronutrient status and avoid toxicity.

The main limitations of this present study are the lack of BMI data, which has prevented full assessment of the prevalence of malnutrition in the retrospective study, and the lack of power analysis caused by the limited sample size in the prospective study. The reasons for the limited sample size in the retrospective study are that childhood cancer incidence is very low, with about 55 patients referred to the RHSC Edinburgh per year. Moreover, during the data collection period the incidence of childhood cancer in South-East Scotland was even lower that the average incidence recorded (51 patients in 18 months) at the RHSC. All these factors have negatively affected the sample size and thus limited the statistical power of the prospective study.

These results highlight the complexity of clinical research and the need for very large numbers of participants to identify the overall risk factors for malnutrition. However, this type of research requires multicentre and even multi-country studies, which can be very lengthy and expensive. Therefore, robust data is required prior to the start of such studies to indicate the number of participants required to achieve clinically meaningful results and to identify the risks factors to be investigated. Therefore, although limited in the sample size, the observational information obtained in this current research is very valuable, especially in consideration that it sets the basis for a further 18 months of data collection. It is hoped that when the prospective study is completed, the 36 months of data collection will provide robust data which can then be validated in larger studies.

These series of studies have highlighted the importance of nutritional screening during childhood cancer therapy. Indeed there is a need for a screening tool to identify children at high medium and low risk of malnutrition. However, considering the extent of nutritional issues that a child can experience during cancer therapy, it is uncertain whether only the high risk children should be having their nutritional status assessed by a dietitian or whether comprehensive monitoring of all of the children treated for cancer is necessary. Until a specific screening tool for this patient group is designed and validated, it would be recommended to assess growth by BMI centile and micronutrient status regularly throughout the treatments. Moreover, children with solid tumour should be monitored with arm anthropometry to avoid the masking effect of tumour mass on weight related measurements. This will ensure that patients requiring NS and supplementation are quickly identified and their progress during NS is monitored.

The findings of this study have underlined areas of investigation for future work. Further studies on the nutritional risk of children with cancer are now required. Most importantly, these studies should have a sample size large enough to allow the identification of specific risk factors for both undernutrition and obesity in paediatric cancer such as age at diagnosis, gender, type of tumour, stage of tumour, treatment modalities, protocols and stage of treatments. If possible such investigations should

be prospective in nature and continue for up to five years. This is important because nutritional issues, especially obesity, may continue well into adulthood. Moreover, intervention studies are now required to evaluate the type of interventions needed to address the modifiable risk factors for obesity such as low physical activity and dietary intake.

Finally, the interaction of cancer treatments, micronutrient status and supplementation must be investigated further, especially to assess the need for supplementation and its safety during cancer therapy. This is important as many patients may develop some micronutrient deficiency and they may need to be supplemented.

In conclusion, this study has shown that children undergoing cancer treatments are at high risk of both undernutrition and obesity and it indicates apparent differences in nutritional risk according to diagnosis and treatment. Moreover it has highlighted the detrimental effect of cancer and its treatments on micronutrient status. Therefore, nutritional status monitoring during childhood cancer therapy is essential and the need for a screening tool specifically designed for this patient group is now pivotal.

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APPENDIX 1

Raquel Revuelta Iniesta
PhD student
Dietetics, Nutrition and Biological Sciences
Queen Margaret University

Sheila Adamson
Collaborations Development Co-ordinator
Queen Margaret University, Edinburgh
Queen Margaret University Drive
Musselburgh
East Lothian EH21 6UU

Direct Dial
Tel (0)131 474 0000 Fax (0)131 474 0001
Email: sadamson@qmu.ac.uk

07 June 2012

Dear Raquel

Request for Ethical Approval for a Research Project – Assessment of reliability, validity and precision between intra and inter observer anthropometrical measurements performed in children and young adults.

Thank you for your response to the letter I sent you following consideration of your application by the Research Ethics Panel.

Professor Nigel Gleeson, Vice-Convener of the Panel, has reviewed your response to the points you were required to address, and has confirmed that he is happy to take Convener's Action to grant full ethical approval for your research.

A standard condition of this ethical approval is that you are required to notify the Panel, in advance, of any significant proposed deviation from the original protocol. Reports to the University are also required once the research is underway if there are any unexpected results or events that raise questions about the safety of the research. Please find the appropriate form for this enclosed.

We would like to thank you for your co-operation and wish you well with your project.

Yours sincerely,

Sheila Adamson
Collaborations Development Co-ordinator

APPENDIX 2

APPENDIX 3

From: Martin, Dawn
Sent: 04 February 2010 09:36
To: Paciarotti, Ilenia
Cc: McKenzie, Jane
Subject: Ethical Approval Application

Dear Ilenia

I am writing to let you know that the Research Ethics Committee considered your application for ethical approval for the following study at yesterday's meeting:

Nutritional Risk in Childhood Cancer

The Committee noted that you have secured ethical approval from the NHS and that separate approval from QMU is not necessary at present. However, should you revise the project in such a way that you require full ethical approval from QMU at any point in the future, you are invited to submit an update of the form directly to me.

Whilst members did not scrutinise the form with a view to rejecting or granting approval, some comments were provided, which I could forward to you if you would consider that helpful. You would not be required to respond or act on these, but the additional feedback may be of interest as the study progresses. If you would like these, please let me know and I will type then up in due course.

Regards

Dawn

Dawn Martin

Assistant Registrar, Quality Enhancement

Queen Margaret University

Edinburgh

EH21 6UU

(0131) 474 0000

dmartin1@qmu.ac.uk

QMU Quality website:

http://www.qmu.ac.uk/services/quality.htm

APPENDIX 4

Queen Margaret University
EDINBURGH

CHILD INVITATION TO PARTICIPATE

"Assessment of reliability, validity and precision of anthropometrical measurements performed in healthy children"

Invitation to take part in the study

- We would like to ask you for help with our study.
- We want to make sure that you understand what is all about before you decide if you would like to take part
- Please talk it over with your mum/dad and take time to decide

What is the study about?

We would like to measure your **weight, height and the thickness of your arm** to help us prepare for a larger project in which children with cancer are involved.

I would recommend wearing **short sleeves** on the day to facilitate taking the measurements.

Will it hurt me?

Taking part will not hurt

Will taking part help me?

Taking part might not help you but you will help the researchers, Ilenia and Raquel, to improve their techniques.

It will also help many children with cancer.

Will anybody know about my

Only the researchers involved in the study as we will not tell anyone else about your measurements

Do I have to take part?

No, this is up to you!

If you don't take part don't worry, that is fine

If you take part but change your mind later on. That is also fine. Just let us know

If you have questions you can speak with:

Raquel Revuelta Iniesta rrevueltainiesta@qmu.ac.uk

Ilenia Paciarotti ipaciarotti@qmu.ac.uk

Dr Jane McKenzie jmckenzie@qmu.ac.uk

Independent advisor (Dr Iain Gow) igow@qmu.ac.uk

Queen Margaret University

EDINBURGH

INFORMATION SHEET FOR PARENTS

"Assessment of reliability, validity and precision of anthropometrical measurements performed in healthy children"

This study will be carried out by Ilenia Paciarotti and Raquel Revuelta Iniesta; we are both PhD students at Queen Margaret University under the supervision of Dr. Jane Mckenzie. The purpose of this project is to assess measurements of body composition in healthy children in preparation for an ongoing project at the Royal Hospital of Sick Children (RHSC), which aims to assess nutritional risk in children with cancer.

We are looking for boys and girls aged between 2 and 18.

- This study will involve:
  - Meeting with the children in a private location: QMU clinic room or other suitable place.
  - The following anthropometrical measurements will be taken on your child twice by each of the researchers:
    - Weight – measured clothed, without shoes, on standing scale
    - Height – measured clothed, without shoes, using a standing height measure
    - Middle upper arm circumference - this involves finding the middle point between the elbow and shoulder and measuring the circumference. Measurements are taken on the non-dominant arm
    - Triceps skinfold- this involves measuring the thickness of the skin on the triceps. For this measurement we use paediatric calipers which pinch the skin gently to measure the thickness
  - Wearing short sleeves will facilitate measurement of the arm.
- Will it hurt my child?
  - Your child should not experience any pain, however the triceps skin fold is sometimes perceived as unpleasant by the children.
- Benefits of taking part
  - This study will not benefit your child directly; however the information obtained will help the researchers to conduct the study performed at the RHSC

- Confidentiality and anonymity
  - All children who take part in the project will be given an identification number and all data will be anonymous.
- Withdrawal
  - You or your child will be able to withdraw from the study at any time without providing any explanation.

- Contact details
  - Researchers' name:
    - Raquel Revuelta Iniesta rrevueltainiesta@qmu.ac.uk
    - Ilenia Paciarotti ipaciarotti@qmu.ac.uk
  - Supervisor:
    - Dr. Jane McKenzie jmckenzie@qmu.ac.uk
  - Independent advisor:
    - If you wish to consult a person who is not involved in this research for independent advice, please contact:
    - Dr. Iain Gow igow@qmu.ac.uk

Queen Margaret University
EDINBURGH

CONSENT FORM

"Assessment of reliability, validity and precision of anthropometrical measurements performed in healthy children"

I confirm that I have read and understood the information sheet for the above study, that I have had the chance to ask questions, and that I have received satisfactory answers to the asked questions. ☐

I understand that my/my child's participation is voluntary and that I am free to withdraw myself/my child at any time, without giving any reason ☐

I agree to have my child take part in the above study ☐

Name of parent/carer Date Signature

Name of child/adolescent Date Signature
(If considered appropriate)

Name of researcher Date Signature

APPENDIX 5

Child Life and Health
Reproductive & Developmental Sciences
Clinical Sciences and Community Health
20 Sylvan Place
EDINBURGH EH9 1UW
Telephone: 0131 536 0615

20th August 2010

PARENT INVITATION TO PARTICIPATE

"Nutritional Risk in Childhood Cancer (prospective study)"

This research project will be carried out by the Royal Hospital for Sick Children, Edinburgh, the University of Edinburgh and Queen Margaret University

The study has the full support and permission of the paediatric haematology and oncology department in Sick Kid's, the Hospital and both Universities.

What is the study about?

Underweight is a major concern in the treatment of children and young people with cancer. Loss of weight or failing to gain weight normally, may occur during the treatment of cancer.

Becoming overweight may be a long-term problem for the survivors of childhood cancer. Children and teenagers who are losing weight or failing to gain weight normally may need additional calories. We realise that these nutritional problems are a source of great stress for families, as we all wish to provide adequate nutrition to our children. Your child will **not** receive any extra tests, procedures or interviews, except we may do slightly more frequent measurements of height or weight, and some extra growth measurements at follow up. We will also check 72 hour food diaries, and wish to record your child's activity levels every 6 months using a special meter worn on a belt around the waist during waking hours.

Why do we need to do the research?

Health services for children and adolescents with cancer depend on the need for those services. Advances come by clinical research. If underweight and overweight really are very common then we would argue for greater provision of services (e.g. dietitians) in order to help children and families. By studying in detail, we will be able to design further appropriate studies for these problems, aiming to improve care.

How will we do this?

We will ask the parents of children who had cancer diagnosed from August 2010 on and are being followed up in SE Scotland if they are willing to take part in the research study.

What is involved for my child?

Your child will **not** receive any extra tests, procedures or interviews, except we will do slightly more frequent measurements of height or weight, and some extra growth measurements in the ward and at follow up. We will also check 72 hour food diaries, and

wish to record your child's activity levels every 6 months using a special meter worn on a belt around the waist during waking hours. We wish to measure your child's quality of life and stress levels (stress levels only if 8 years or older) by means of a questionnaire.

What is involved for me?

We wish to measure your thoughts on your child's quality of life by means of the same quality of life (PedsQL) questionnaire. We also wish to measure the effects that your child having cancer has caused you, measuring your stress levels, emotional and physical health by means of a 2nd questionnaire (the SF36), this should take 5-10 minutes to fill in, although you may find filling in the forms time-consuming or tiresome.

Lastly, to obtain more information about parent and carer issues with nutritional care, we will invite some parents to share their views with us by either having one to one interviews with a qualified research team member, or taking part in a focus group run by a qualified research team member. These interviews will be tape recorded and transcribed (the words typed) so that the researchers can look at what everyone said. You and your child will not be able to be identified from any information gained from these recordings.

Where do I have to go?

All the measures will be made at your child's follow up visits or during admission to RHSC.

If you or your child want to opt in to the study it is entirely up to you. Your child's care will not be affected by whether or not you take part. If you/your child agree to take part but want to opt out later that is also fine and it will not affect your child's care.

If you have any questions or would like a more detailed explanation of the study, please contact:

Dr David Wilson (Sick Children's Hospital Edinburgh) Tel: (0131-536-0615)

CHILD INVITATION TO PARTICIPATE

"Nutritional Risk in Childhood Cancer (prospective study)"

(To be read to children by their parents where necessary)

Invitation to Take Part in the Study – What is it all about?

We would like to ask you for help with our research project.

We want you to understand all about it before you decide if you want to help or not.

Please talk it over with your Mum/Dad and take time to decide what you want to do.

What is the Study About?

Getting underweight can happen if you get cancer and some kids and teenagers then get overweight later. We want to find out more about these problems.

What Will Happen if I Agree to Take Part?

At follow up we will measure your height and weight as usual, and the thickness of your arm. We will also check some food diaries, and measure your activity levels every 6 months using a special meter worn on a belt around the waist during waking hours. We wish to measure what having cancer does to your life by means of some questions on a form called a questionnaire, and we will also ask your parents to fill in a similar form.

We will not tell anyone else about your measurements or results

Will it Hurt Me?

Taking part will not hurt.

Will Taking Part Help Me?

Taking part might not help you but should help other children and teenagers in future

Who Will Know I Have Taken Part?

Only the researchers involved in the study.

Do I Have To Take Part?

No – this is up to you. If you don't take part don't worry, that is fine.

If you do take part and change your mind, don't worry – that is also fine. Just let us know.

Who do I Speak to if I Have Any Questions ?

Dr David Wilson (Tel: 0131-536 0615)

Reproductive & Developmental Sciences

Clinical Sciences and Community Health

20 Sylvan Place

EDINBURGH EH9 1UW

Telephone: 0131 536 0801

Study Number:

Patient Identification Number for this trial:

CONSENT FORM – child 8 to 12 years

Title of Project:

"Nutritional Risk in Childhood Cancer (prospective study)".

Name of Principal Researcher: Dr David C Wilson

Please initial box

I have read or my family have read out to me the study information sheet,

I have had the chance to ask questions and ☐

I am happy with answers to the questions that I have asked.

I understand that my taking part is up to me and that I am can

stop at any time, and the doctors will go on treating me in the way ☐

they think is best for me.

3. I agree to take part in the above study. ☐

_____ _____ _____

Name Date Signature

_____ _____ _____

Name of Person providing information Date Signature

(if different from researcher)

_____ _____ _____

Researcher Date Signature

(Investigator or delegated medically qualified co-investigator)

1 for child, 1 for researcher; 1 to be kept with hospital notes

Date: 20th August, 2010 **Version number: Second**

Child Life and Health

Reproductive & Developmental Sciences

Clinical Sciences and Community Health

20 Sylvan Place

EDINBURGH EH9 1UW

Telephone: 0131 536 0801

Study Number:

Patient Identification Number for this trial:

CONSENT FORM – child less than 8 years

Title of Project:

"Nutritional Risk in Childhood Cancer (prospective study)".

Name of Principal Researcher: Dr David C Wilson

Please initial box

I have read or my family have read out to me the study information sheet,

I have had the chance to ask questions and ☐

I am happy with answers to the questions that I have asked.

I know that I don't have to help unless I want to. If I start, I can

stop at any time. The doctors will still try hard to make me better. ☐

3. I agree to take part in the above study. ☐

_____ _____ _____

Name Date Signature

_____ _____ _____

Name of Person providing information Date Signature

(if different from researcher)

_____ _____ _____

Researcher Date Signature

(Investigator or delegated medically qualified co-investigator)

1 for child, 1 for researcher; 1 to be kept with hospital notes

Date: 20th August, 2010 **Version number: Second**

Child Life and Health

Reproductive & Developmental Sciences

Clinical Sciences and Community Health

20 Sylvan Place

EDINBURGH EH9 1UW

Telephone: 0131 536 0801

Study Number:

Patient Identification Number for this trial:

CONSENT FORM

Title of Project:

"Nutritional Risk in Childhood Cancer (prospective study)".

Name of Principal Researcher: Dr David C Wilson

Please initial box

I confirm that I have read and understand the information sheet for the above study, that I have had the opportunity to ask questions, and that I have received satisfactory answers to the questions that I have asked. ☐

I understand that my child's participation is voluntary and that I am free

to withdraw my child at any time, without giving any reason, without ☐

my infant's medical care or legal rights being affected.

3. I agree to have my infant take part in the above study. ☐

4. If asked I agree to take part in audio-taped interviews. ☐

_____ _____ _____

Name of Parent/Carer Date Signature

_____ _____ _____

Name of Person providing information Date Signature

(if different from researcher)

_____ _____ _____

Researcher Date Signature

(Investigator or delegated medically qualified co-investigator)

1 for parent/carer, 1 for researcher; 1 to be kept with hospital notes

Date: 20th August, 2010 **Version number: Third**

APPENDIX 6

Activity Diary

Name:

Date:

Study code:

Please wear the activity monitor for the next 7 days. You can choose to use the sticky pad or the belt to wear the activity monitor as shown to you by Ilenia the research nutritionist. The sticky pad should be placed over the monitor and secured on to the abdomen.The belt should be tied around /your child's waist. The red monitor sits on the right hand side as shown by Ilenia.

Put the activity monitor on first thing in the morning and record when you/ your child started to wear it under 'Time ON'.

Take the activity monitor off at bed time and record when you/ your child stopped wearing it under 'Time OFF'

If you/ your child remove the activity monitor at any other time during the day please note these over the page.

DAY	TIME ON	TIME OFF
1		
2		
3		
4		
5		
6		
7		

Please return activity monitor and this diary to Ilenia Paciarotti or Kerry White.

Instructions for activity monitor

You can choose to wear the activity monitor with an elastic belt or by placing a sticky pad over it to secure it in place. The activity monitor should be situated on the right hip under yours / your child's waist with the black button at the top and Actigraph logo along the bottom.

The activity monitor is set to record activity; you do not need to switch it on or off. Follow the instructions below for wearing the activity monitor:

1. Place the elastic belt around yours/ your child's waist if worn by belt, pull the elastic until the belt is secure and comfortable then tie and pull the belt buckle or place a new sticky pad "Tegaderm" over the activity monitor to secure it on the right hip under yours/ your child's clothes.
2. Make sure that the black button is at the top of the activity monitor and the Actigraph logo runs along the bottom.
3. Record the time you/your child started to wear the activity monitor in the "Activity Diary"
4. You/Your child should wear the activity monitor all day, but the activity monitor must be removed if you/your child is having a shower/ bath or going swimming and those activity should be noted on the "Activity Diary".
5. Remove the activity monitor at bed-time , if worn by sticky pad dispose the Tegaderm.
6. Record the time your child stopped wearing the activity belt in the "Activity Diary".
7. Please return the activity monitor to Ilenia Paciarotti or Kerry White in the envelope provided either leaving it on the ward or posting it.

Thank you!

APPENDIX 7

List of Publications

Abstracts

I Paciarotti, J McKenzie, M Brougham, A Edgar, M Wilson, L Stewart, A Ling Koh, D C. Wilson. Children with cancer have high needs for nutrition support.2012. *Clinical Nutrition,*7 (S1),pp. 79

Poster presented at the ESPEN Congress 2012

Ilenia Paciarotti, R. Revuelta Iniesta, J. McKenzie , M. Brougham , D.C.Wilson *Outstanding Abstract*. Low plasma vitamin D (25-hydroxycholecalciferol) in Scottish children and adolescents diagnosed with cancer. 2012. *Clinical Nutrition,*7 (S1),pp. 157

Poster presented at the ESPEN Congress 2012

R. Revuelta Iniesta, **I Paciarotti** , M. Brougham , J. McKenzie , D C. Wilson Systematic review of the prevalence of malnutrition in childhood cancer: effects of cancer and its treatments on nutritional status

Poster submitted to the ESPEN Congress 2013

Articles

I Paciarotti, J McKenzie, M Brougham, A Edgar, M Wilson, L Stewart, A Ling Koh, D C. Wilson. Children with cancer have high needs for nutrition support.2012. *In submission*

Ilenia Paciarotti , R. Revuelta Iniesta , J. McKenzie , M. Brougham , D. C. Wilson *Outstanding Abstract*. Low plasma vitamin D (25-hydroxycholecalciferol) in Scottish children and adolescents diagnosed with cancer. *In preparation*

R. Revuelta Iniesta, **I Paciarotti** , M. Brougham , J. McKenzie , D.C Wilson Systematic review of the prevalence of malnutrition in childhood cancer: effects of cancer and its treatments on nutritional status *In preparation*

Ilenia Paciarotti , J. McKenzie , M. Brougham , D C. Wilson Short term effects of childhood cancer and its treatments on nutritional status and growth, a prospective study. *In preparation*